CASE 4-20918/-/CIP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV722485614US	December 20, 2005
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 6,465,504 B1

ISSUED: OCTOBER 15, 2002

INVENTORS: RENÉ LATTMANN, PIERRE ACKLIN

FOR: SUBSTITUTED 3,5-DIPHENYL-1,2,4-TRIAZOLES AND THEIR USE AS PHARMACEUTICAL METAL CHELATORS

MS Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C.§156

Sir:

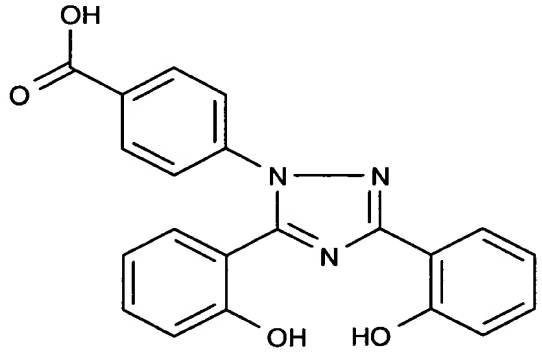
Pursuant to 35 U.S.C.§156 and 37 C.F.R.§1.710 *et seq.*, Novartis AG ("Applicant"), a Corporation organized under the laws of Switzerland, hereby requests an extension of the patent term due to regulatory review of U.S. Patent No. 6,465,504 B1, which was granted on October 15, 2002.

Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 6,465,504 B1 by virtue of an assignment from the inventors, René Lattmann and Pierre Acklin, to Novartis AG. The assignment from the inventors is recorded in the U.S. Patent and Trademark Office at Reel 013242, Frame 0372 on August 28, 2002. A copy of the assignment is attached hereto as Appendix A. A copy of the Power of Attorney evidencing that Novartis AG being the owner of the entire right, title and interest in and to U.S. Patent No. 6,465,504 appoints Oona A. Jackson, as its agent to act in its interest in this matter is attached hereto as Appendix B.

In accordance with 35 U.S.C.§156 and 37 C.F.R.§1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are numbered analogously to 37 C.F.R.§1.740.

(1) Identification of the Approved Product

The approved product is Exjade®, which contains the active ingredient deferasirox, having the chemical name 4-[3,5-bis(2-hydroxyphenyl)-[1,2,4]triazol-1-yl]benzoic acid and having the chemical structure



2. Identification of the Federal Statute under which Regulatory Review Occurred

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505(b)(2) (21 U.S.C.§355(b)(2)).

3. The Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C.§355(c)) on November 2, 2005. A copy of the FDA approval letter is attached hereto as Appendix C.

4. Active Ingredient Statement

The sole active ingredient in Exjade® is deferasirox, which has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the

Public Health Service Act, or the Virus-Serum Toxin Act prior to the approval of NDA 21-882 by the United States Food and Drug Administration on November 2, 2005.

5. Statement of Timely Filing

The last day on which this application could be submitted is January 1, 2006, which is 60 days after the approval of NDA 21-882 on November 2, 2005. This application is timely filed on or prior to January 1, 2006.

6. Identification of Patent for which Extension is Sought

This application seeks to extend the term of U.S. Patent No. 6,465,504 B1, which issued October 15, 2002 to René Lattmann and Pierre Acklin, the term of which would otherwise expire on June 24, 2017.

7. Patent Copy

A complete copy of U.S. Patent No. 6,465,504 B1, identified in paragraph 6 above, is attached as Appendix D.

8. Post-Issuance Activity Statement

No Reexamination certificate or Reissue has been issued or requested with respect to U.S. Patent No. 6,465,504 B1.

A Request for a Certificate of Correction under 37 C.F.R. §1.322 for U.S. Patent No. 6,465,504 B1 was received by the United States Patent and Trademark Office on June 3, 2003. A copy of the Request is attached hereto as Appendix E. A review of our files has indicated that the Request has not been granted as of the date of this Patent Term Extension Request.

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

Claims 1-6, 8 and 9 cover the approved product, Exjade®, the active ingredient of which is deferasirox, in the form of a dissolvable tablet in strengths containing 125 mg, 250 mg or 500 mg of active ingredient.

Claims 1-3 claim compounds, including deferasirox, the active ingredient in the approved product. The active ingredient, deferasirox, is the compound of claim 1 wherein R_1, R_2, R_4 and R_5 are hydrogen, and R_3 is an aryl substituted by one carboxyl substituent in the 4 position.

Claim 4 claims several compounds by their chemical name, including the active ingredient of Exjade®, which is 4-[3,5-bis(2-hydroxyphenyl)-[1,2,4]triazol-1-yl]benzoic acid. Claim 5 claims the active ingredient of the approved product by its chemical name, which is 4-[3,5-bis(2-hydroxyphenyl)-[1,2,4]triazol-1-yl]benzoic acid.

Claims 6, 8 and 9 claim pharmaceutical compositions containing deferasirox, the active ingredient of the approved product. Claim 6 claims a pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1. Claim 8 defines the pharmaceutical composition of claim 6 as comprising the active ingredient of Exjade® by its chemical name, which is 4-[3,5-bis(2-hydroxyphenyl)-[1,2,4]triazol-1-yl]benzoic acid. Claim 9 claims a pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 4.

10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C.§156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) The patent for which extension of the term thereof is sought claims a human drug product. The human drug product is a composition containing deferasirox.

(A) An Investigational New Drug Application for deferasirox was submitted on June 30, 1999, was received by the Department of Health and Human Services on July 1, 1999, was assigned IND No. 58,554, and became effective on July 31,1999. The original IND was filed for iron chelation. A copy of the IND letter from the FDA is attached as Appendix F.

(B) A New Drug Application for Exjade® was received by the Department of Health and Human Services on May 2, 2005 and granted NDA No. 21-882.

(C) NDA No. 21-882 was approved on November 2, 2005.

11. Brief Description of Activities Undertaken During the Regulatory Review Period

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as Appendix F is a chronology of the major communications between the U.S. Food and Drug Administration and the Applicant in IND No. 58,554 and NDA No. 21-882.

12. Opinion of Eligibility for Extension

Applicant is of the opinion that U.S. Patent No. 6,465,504 B1 is eligible for extension under 35 U.S.C.§156 and 37 C.F.R.§1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C.§156(a) and 37 C.F.R.§1.720(a)

U.S. Patent No. 6,465,504 B1 claims, deferasirox, the active ingredient of a human drug product and pharmaceutical compositions containing the active ingredient. MPEP 2751 states:

> "A patent is considered to claim the product at least in those situations where the patent claims the active ingredient per se, or claims a composition or formulation which contains the active ingredient(s) and reads of the composition or formulation approved for commercial marketing or use"

(b) 35 U.S.C.§156(a)(1) and 37 C.F.R.§1.720(g)

The term of U.S. Patent No. 6,465,504 B1 (expiring June 24, 2017) has not expired before the submission of this application.

(c) 35 U.S.C.§156(a)(2) and 37 C.F.R.§1.720(b)

The term of U.S. Patent No. 6,465,504 B1 has never been extended.

(d) 35 U.S.C.§156(a)(3) and 37 C.F.R.§1.720(c)

The application for extension of the term of U.S. Patent No. 6,465,504 B1 is submitted by the authorized attorney of the owner of record thereof in accordance with the requirements of 35 U.S.C.§156(d) and 37 C.F.R.§1.740.

(e) 35 U.S.C.§156(a)(4) and 37 C.F.R.§1.720(d)

The approved product, Exjade®, has been subjected to a regulatory review period before its commercial marketing or use.

(f) 37 C.F.R.§1.720(h)

No other patent has been extended for the same regulatory review period for the approved product, Exjade®.

(g) 35 U.S.C.§156(a)(5)(A) and 37 C.F.R.§1.720(e)(1)

The permission for the commercial marketing or use of the approved product, Exjade® is the first received permission for commercial marketing or use of Exjade® under the provision of law under which the applicable regulatory review occurred.

13. Length of extension claimed under 37 C.F.R.§1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. 6,465,504 B1 requested by Applicant is 648 days, which length was calculated in accordance with 37 C.F.R.§1.775 as follows:

(a) The regulatory review period under 35 U.S.C.§156(g)(1)(B) began on July 31, 1999 (the effective date of the IND) and ended on November 2, 2005, amounting to a total of 2285 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C.§156(g)(1)(B)(i), the "Testing Period," began on July 31, 1999 and ended on May 2, 2005 which is 2101 days;

(ii) The period for review under 35 U.S.C.§156(g)(1)(B)(ii), the "Application Period," began on May 2, 2005 and ended on November 2, 2005, which is 184 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (13)(a) above (2285 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (October 15, 2002), i.e., 1173 days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., zero days, and

(iii) One-half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one-half of (2101 - [1173 + 0]) or 464 days;

which results in a period of 2285 -[1173 + 0 + 464 days] = 648 days.

(c) The number of days as determined in subparagraph (13)(b), when added to the original term (June 24, 2017), would result in the date of April 3, 2019.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (November 2, 2005) would result in the date of November 2, 2019.

(e) The earlier date as determined by subparagraphs (13)(c) and (13)(d) is April 3, 2019.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 6,465,504 B1 (June 24, 2017), results in the date June 24, 2022.

(g) The earlier date as determined in subparagraphs (13)(e) and (13)(f) is April 3, 2019.

14. Duty of Disclosure Acknowledgement Under 37 C.F.R.§1.740(a)(13)

Applicant acknowledges a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

15. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

16. Correspondence Address Required by 37 C.F.R.§1.740(a)(15)

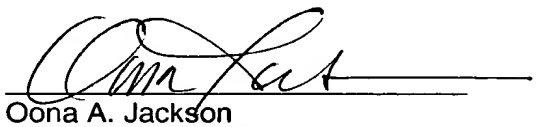
All correspondence relating to this application for patent term extension should be addressed to:

Novartis
Corporate Intellectual Property
One Health Plaza, Bldg. 104
East Hanover, NJ 07936-1080

17. Certification Under 37 C.F.R.§1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof in accordance with 37 C.F.R.§1.740(b).

Respectfully submitted,



Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Oona A. Jackson
Attorney for Applicant
Reg. No. 48,152
(862) 778-7852

Date: December 20, 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

APPENDIX A

DEC 2002
RECEIVED
Linda C. Rothwell
Patent

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

DECEMBER 03, 2002

NOVARTIS CORPORATION
THOMAS HOXIE
564 MORRIS AVENUE
PATENT AND TRADEMARK DEPT.
SUMMIT, NJ 07901-1027

102292846A

CORRECTED NOTICE

UNITED STATES PATENT AND TRADEMARK OFFICE
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RECORDATION DATE: 08/28/2002

REEL/FRAME: 013242/0372
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
LATTMANN, RENE

DOC DATE: 01/22/2001

ASSIGNOR:
ACKLIN, PIERRE

DOC DATE: 01/23/2001

ASSIGNEE:
NORVARTIS AG
SCHWARZWALDALLEE 215
BASEL, SWITZERLAND 4058

SERIAL NUMBER: 09699765
PATENT NUMBER: 6465504

FILING DATE: 10/30/2000
ISSUE DATE: 10/15/2002

PEARLENE FOSTER, PARALEGAL
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

ENTERED 12/19/02

FORM PTO-1595 (Rev. 6-93) 8/28/02 RECORDATION FORM COVER SHEET

11-26-2002

OMB No. 0651-0011 (exp. 4/94) **PATENTS ONLY 4-20918B/N1**

102292846

To the Honorable Commissioner of Patents and Trademarks: Please record the attache[illegible] copy thereof.

1. Name of conveying party(ies):

   1) Rene Lattmann and 2) Pierre Acklin

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

   Name: Novartis AG

   Internal Address: _____

   Street Address: Schwarzwaldallee 215

   City: Basel State: Switzerland ZIP: 4058

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

   ☒ Assignment ☐ Merger

   ☐ Security Agreement ☐ Change of Name

   ☐ Other _____

Execution Date: 1) January 22, 2001 and 2) January 23, 2001

4. Application number(s) or patent number(s):

   If this document is being filed together with a new application, the execution date of the application is: _____

   A. Patent Application No.(s)
   09/699,765

   B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

   Name: Thomas Hoxie

   Internal Address: Novartis Corporation

   Patent and Trademark Dept.

   Street Address: 564 Morris Avenue

   City: Summit State: NJ ZIP: 07901-1027

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $ 40

   ☐ Enclosed

   ☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

   19-0134 (in the name of Novartis Corporation)

   (Attach duplicate copy of this page if paying by deposit account)

09/04/2002 GTON11 00000262 190134 09699765

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Joseph J. Borovian
Name of Person Signing
Reg. No. 26,631

Joseph J. Borovian
Signature

August 28, 2002
Date

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Washington, D.C. 20231

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Case **4-20918B/N1**

ASSIGNMENT

I / We **René Lattmann, Rottmanbodenstr. 133, 4102 Binningen,Switzerland**
Pierre Acklin, Markgraeflerstr. 47, 4057 Basel, Switzerland

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to ***Novartis AG, a Company organized under the laws of the Swiss Confederation, of Schwarzwaldallee 215, 4058 Basel, Switzerland***, its successors, assigns and legal representatives all my/our right, title and interest, in and for the United States of America, in and to the invention entitled:

SUBSTITUTED 3,5-DIPHENYL-1,2,4-TRIAZOLES AND THEIR USE AS PHARMACEUTICAL METAL CHELATORS

invented by me/us and described in the application for United States Letters Patent therefor,

Serial No. **09/699,765** filed **October 30, 2000**

and all United States Letters Patent which may be granted therefor, and all divisions, reissues, continuations and extensions thereof, the said interest being the entire ownership of the said Letters Patent when granted, to be held and enjoyed by the said ***Novartis AG***, its successors, assigns or other legal representatives, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by me/us if this assignment and sale had not been made;

And I/we hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to the said ***Novartis AG***.

Signed on

X _____ X January 22, 2001
René Lattmann

X _____ X January 23, 2001
Pierre Acklin

FORM PTO-1595 (Rev. 6-93)

OMB No. 0651-0011 (exp. 4/94)

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PATENTS ONLY 4-20918B/N1

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

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1. Name of conveying party(ies):

   1) Rene Lattmann and 2) Pierre Acklin

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☒ Other **Please correct the Notice of Recordation of Assignment . The executed date for Pierre Acklin should read 01/23/2001: The assignment could be found on Reel/Frame 013242/0372.**

Execution Date: 1) January 22, 2001 and 2) January 23, 2001

2. Name and address of receiving party(ies)

Name: Novartis AG

Internal Address: _____

Street Address: Schwarzwaldallee 215

City: Basel State: Switzerland ZIP: 4058

Additional name(s) & address(es) attached? ☐ Yes ☒ No

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09/699,765

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Thomas Hoxie

Internal Address: Novartis Corporation

Patent and Trademark Dept.

Street Address: 564 Morris Avenue

City: Summit State: NJ ZIP: 07901-1027

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $_____

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

19-0134 (in the name of Novartis Corporation)

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To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Joseph J. Borovian — Name of Person Signing
Reg. No. 26,631

Signature

November 20, 2002
Date

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09-05-2002

OMB No. 0651-0011 (exp. 4/94) **PATENTS ONLY 4-20918B/N1**

102212667

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1. Name of conveying party(ies):
   1) Rene Lattmann and 2) Pierre Acklin

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

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01:581 40.00 CH

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Name of Person Signing
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Signature

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Date

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FINANCE SECTION

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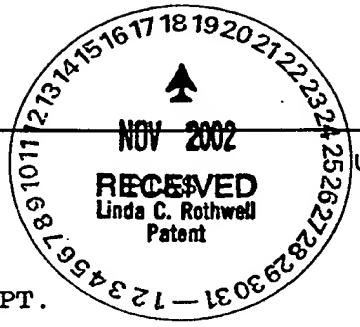

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

NOVEMBER 14, 2002

NOVARTIS CORPORATION
THOMAS HOXIE
564 MORRIS AVENUE
PATENT AND TRADEMARK DEPT.
SUMMIT, NJ 07901-1027

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LATTMANN, RENE

DOC DATE: 01/22/2001

ASSIGNOR:
ACKLIN, PIERRE

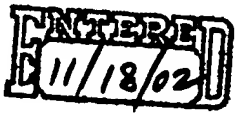
DOC DATE: 01/23/2002

ASSIGNEE:
NORVARTIS AG
SCHWARZWALDALLEE 215
BASEL, SWITZERLAND 4058

SERIAL NUMBER: 09699765
PATENT NUMBER: 6465504

FILING DATE: 10/30/2000
ISSUE DATE: 10/15/2002

VIOLET MCCOY, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS



Case **4-20918B/N1**

ASSIGNMENT

I / We **René Lattmann, Rottmanbodenstr. 133, 4102 Binningen,Switzerland**
Pierre Acklin, Markgraeflerstr. 47, 4057 Basel, Switzerland

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to ***Novartis AG, a Company organized under the laws of the Swiss Confederation, of Schwarzwaldallee 215, 4058 Basel, Switzerland***, its successors, assigns and legal representatives all my/our right, title and interest, in and for the United States of America, in and to the invention entitled:

SUBSTITUTED 3,5-DIPHENYL-1,2,4-TRIAZOLES AND THEIR USE AS PHARMACEUTICAL METAL CHELATORS

invented by me/us and described in the application for United States Letters Patent therefor,

Serial No. **09/699,765** filed **October 30, 2000**

and all United States Letters Patent which may be granted therefor, and all divisions, reissues, continuations and extensions thereof, the said interest being the entire ownership of the said Letters Patent when granted, to be held and enjoyed by the said ***Novartis AG***, its successors, assigns or other legal representatives, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by me/us if this assignment and sale had not been made;

And I/we hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to the said ***Novartis AG.***

Signed on

X René Lattmann — X January 22, 2001
René Lattmann

X Pierre Acklin — X January 23, 2001
Pierre Acklin

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 6,465,504 B1

ISSUED: OCTOBER 15, 2002

INVENTORS: RENÉ LATTMANN, PIERRE ACKLIN

FOR: SUBSTITUTED 3,5-DIPHENYL-1,2,4-TRIAZOLES AND THEIR USE AS PHARMACEUTICAL METAL CHELATORS

MS Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA, 22313-1450

POWER OF ATTORNEY

Sir:

Novartis AG, a company organized and existing under the laws of the Swiss Confederation, having a place of business at Lichtstrasse 35, Basle, Switzerland 4056, being the owner of the entire right, title and interest in and to U.S. Patent No. 6,465,504 which was granted on October 15, 2002 to René Lattmann and Pierre Acklin and entitled "substituted 3,5-Diphenyl-1,2,4-Triazoles and Their Use as Pharmaceutical Metal Chelators" hereby appoints the undersigned, Oona A. Jackson, as its agent to act in its interest in this matter, and also appoints the attorneys and agents associated with Customer No. 001095, respectively and individually, each of them with full power of substitution and revocation, with regard to an application for extension of the term of U.S. Patent No. 6,465,504 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please direct all telephone calls to Oona A. Jackson at (862) 778-7852, and all correspondence to Richard Gearhart at Novartis, Corporate Intellectual Property, One Health Plaza, Building 104, East Hanover, New Jersey 07936-1080.

Novartis AG

By: P E Crawley

Name: P.E. CRAWLEY

Title: Authorised Signatory

By:

Name V. LARDANS

Title: Authorised Signatory.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-882

Novartis Pharmaceuticals Corporation
Attention: Susan P. Nemeth, Ph.D.
One Health Plaza
Hanover, NJ 07936-1080

Dear Dr. Nemeth:

Please refer to your new drug application (NDA) dated April 29, 2005, received May 2, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exjade® (deferasirox) Tablets for Oral Suspension.

We acknowledge receipt of your submissions dated May 10, May 23, May 27, June 29, July 8, July 11, July 12, July 28, August 15, August 29, September 16, September 20, October 21, October 27, October 31, November 1, and November 2, 2005.

This new drug application provides for the use of Exjade® (deferasirox) Tablets for Oral Suspension for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted November 2, 2005) and submitted labeling (immediate container labels submitted October 27, 2005). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-882.**" Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your

postmarketing study commitments specified in your submission dated November 2, 2005. These commitments, along with any completion dates agreed upon, are listed below.

1. Establish a registry for children aged 2 to < 6 years to enroll approximately 200 patients and follow them for 5 years. Data collection will be at least monthly for renal function and blood pressure and yearly for growth and development. Submit your monitoring scheme for our review and comment.

   Protocol Submission: by June 30, 2006
   Study Start: by December 31, 2006
   Final Report Submission: by June 30, 2012

2. Complete the extension portion of Studies 0105E2, 0106E1, 0107E1, 0108E1, and 0109E1 for a total of 4 years after the core trial (5 years total in patients initially treated with ICL670, 4 years for patients initially treated with DFO).

   Amendment Submission: by January 31, 2006
   Study Start: N/A (ongoing)
   Final Report Submission: by June 30, 2009

3. Conduct a single arm study in patients with congenital or acquired anemias and chronic iron overload to obtain additional data in patients with LIC < 7 treated with Exjade® doses of 20 or 30 mg/kg per day.

   Protocol Submission: by June 30, 2006
   Study Start: by December 31, 2006
   Final Report Submission: by March 31, 2010

4. Provide the full study report, including safety and efficacy datasets, for Study 0109, a study in patients with sickle cell disease.

   Final Report Submission: by January 31, 2006

5. Provide an adequate proposal for assessing iron concentration and cardiac function in patients treated with Exjade®.

   Protocol Submission: by January 31, 2006
   Study Start: by April 30, 2006
   Final Study Report: by June 30, 2008

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated **"Subpart H Postmarketing Study Commitments."**

In addition, we note your following postmarketing study commitments, specified in your submission dated November 2, 2005, that are not a condition of the accelerated approval. These commitments are listed below:

6. Complete a study to collect safety and efficacy data for Exjade® in patients with elevated baseline serum creatinine (≥ 2X ULN) in patients with low or intermediate risk MDS (e.g., Study US03, amended to include patients with baseline serum creatinine values up to 2X ULN). Duration of followup on Exjade® should be at least 3 years.

   Amendment Submission: by January 31, 2006
   Study Start: by N/A (ongoing)
   Final Report Submission: by December 31, 2009

7. Conduct a single dose pharmacokinetics study of Exjade® in subjects with hepatic impairment.

   Protocol Submission: by March 31, 2006
   Study Start: by June 30, 2006
   Final Report Submission: by June 30, 2007.

8. Conduct a drug-drug interaction study with midazolam to investigate the potential of Exjade® to inhibit CYP4503A4.

   Protocol Submission: by March 31, 2006
   Study Start: by June 30, 2006
   Final Report Submission: by June 30, 2007

9. Complete study of long-term follow-up (3 years) in 150 patients with myelodysplastic syndromes (MDS) receiving Exjade® to evaluate safety (including cardiac, hepatic, endocrine and renal) and hematologic and clinical benefit of Exjade® in these patients.

   Amendment Submission: by January 31, 2006
   Study Start: N/A (ongoing)
   Final Report Submission: by December 31, 2009

10. Conduct an ophthalmologic study in patients receiving Exjade®. Examinations should include distance visual acuity, applanation tonometry, lens photography, and wide angle fundus photography of retina and optic nerve and should be done at baseline (prior to Exjade® initiation) and at six month intervals. At least 60 patients should complete 2 years of follow-up.

    Protocol Submission: by June 30, 2006
    Study Start: by December 31, 2006
    Final Report Submission: by March 31, 2010

11. Adequately address the high specification limit of 5 ppm for maximum allowable level of 4-Hydrazinobenzoic acid (4-HBA) in the drug substance. To qualify the presence of this impurity of 5 ppm, conduct a 4-week repeated dose oral toxicity study with 4-HBA in rats and demonstrate that the no effect dose is at least 50 ppm, i.e., ≥10 fold higher concentration than the proposed qualification level of 5 ppm. The study should employ pure 4-HBA. (Refer to the ICH Q3A document entitled, "Guidance on Impurities in New Drug Substances, February 2003).

    Protocol Submission: by January 31, 2006
    Study Start: by May 31, 2006
    Final Study Submission: by December 31, 2006

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Division of Drug Marketing, Advertising and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Although not required, we have the following additional recommendations/requests:

- You are planning a one year trial (study 2409) that will examine the efficacy and safety of Exjade® in about 1500 patients with chronic iron overload due to blood transfusions. Consider incorporating evaluation of cardiac iron and cardiac function, as well as clinical outcomes, to explore relationship amongst LIC, cardiac iron, serum ferritin and clinical endpoints.

- Recognizing that there may be a subset of patients who may not experience sufficient decreases in body iron burden at highest recommended doses of Exjade®, or who cannot tolerate Exjade®, should such a population emerge, consider conducting a study of some combination of deferoxamine and Exjade.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

EXJADE®

(deferasirox)

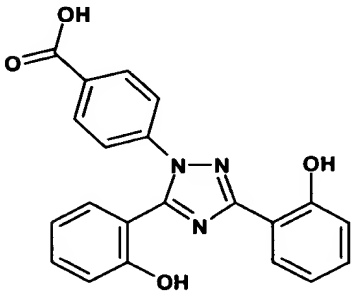
Tablets for Oral Suspension

Rx only

Prescribing Information

DESCRIPTION

EXJADE® (deferasirox) is an iron chelating agent. EXJADE tablets for oral suspension contain 125 mg, 250 mg, or 500 mg deferasirox. Deferasirox is designated chemically as 4-[3,5-Bis (2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-benzoic acid and its structural formula is



Deferasirox is a white to slightly yellow powder. Its molecular formula is $C_{21}H_{15}N_3O_4$ and its molecular weight is 373.4.

Inactive Ingredients: Lactose monohydrate (NF), crospovidone (NF), povidone (K30) (NF), sodium lauryl sulphate (NF), microcrystalline cellulose (NF), silicon dioxide (NF), and magnesium stearate (NF).

CLINICAL PHARMACOLOGY

General

Mechanism of action/Pharmacodynamics

EXJADE® (deferasirox) is an orally active chelator that is selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

Pharmacodynamic effects tested in an iron balance metabolic study showed that deferasirox (10, 20 and 40 mg/kg/day) was able to induce a mean net iron excretion (0.119, 0.329 and 0.445 mg Fe/kg body weight/d, respectively) within the clinically relevant range (0.1-0.5 mg/kg/day). Iron excretion was predominantly fecal.

The effect of 20 and 40 mg/kg of deferasirox on QT interval was evaluated in a single-dose, double-blind, randomized, placebo-and active-controlled (moxifloxacin 400 mg), parallel group study in 182 healthy male and female volunteers aged 18-65 years. No evidence of prolongation of the QTc interval was observed in this study.

Pharmacokinetics

Absorption

EXJADE® (deferasirox) is absorbed following oral administration with median times to maximum plasma concentration (t_{max}) of about 1.5 to 4 hours. The C_{max} and AUC of deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to deferasirox increased by an accumulation factor of 1.3 to 2.3 after multiple doses. The absolute bioavailability (AUC) of deferasirox tablets for oral suspension is 70% compared to an intravenous dose.

Distribution

Deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state (V_{ss}) of deferasirox is 14.37 ± 2.69 L in adults.

Metabolism

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalysed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). No evidence for induction or inhibition of enzymes at therapeutic doses has been observed.

Excretion

Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox and metabolites is minimal (8% of the administered dose). The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours following oral administration.

Special Populations

Renal Insufficiency: Deferasirox is minimally (8%) excreted via the kidney. EXJADE has not been studied in patients with renal impairment. (See also PRECAUTIONS, Laboratory Tests, ADVERSE REACTIONS).

Hepatic Insufficiency: Deferasirox is principally excreted by glucuronidation and is minimally (8%) metabolised by oxidative cytochrome P450 enzymes. EXJADE has not been studied in patients with hepatic impairment. EXJADE treatment has been initiated in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. The pharmacokinetics of deferasirox were not influenced by such transaminase levels.

Pediatric/Geriatric Patients: Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox was less than in adult patients. In children < 6 years of age, systemic exposure was about 50% lower than in adults-(See PRECAUTIONS, Pediatric Use). The pharmacokinetics of deferasirox have not been studied in geriatric patients (65 years of age or older).

Gender: Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males.

CLINICAL STUDIES

The primary efficacy study, Study 1, was a multi-center, open-label, randomized, active comparator control study to compare EXJADE® (deferasirox) and deferoxamine in patients with β-thalassemia and transfusional hemosiderosis. Patients ≥2 years of age were randomized in a 1:1 ratio to receive either oral EXJADE at starting doses of 5, 10, 20 or 30 mg/kg once daily or subcutaneous Desferal® (deferoxamine) at starting doses of 20 to 60 mg/kg for at least 5 days per week based on LIC (liver iron concentration) at baseline (2-3, >3-7, >7-14 and >14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values <7 mg Fe/g dry weight were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of ≥ 3 mg Fe/g dry weight for baseline values ≥ 10 mg Fe/g dry weight, reduction of baseline values between 7 and < 10 to < 7 mg Fe/g dry weight, or maintenance or reduction for baseline values <7 mg Fe/g dry weight.

A total of 586 patients were randomized and treated, 296 with EXJADE and 290 with deferoxamine. The mean age was 17.1 years (range, 2-53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (EXJADE n=276; deferoxamine n=277) who had LIC evaluated at baseline and 12 months or discontinued due to an AE. The percentage of patients achieving the primary endpoint was 52.9% for EXJADE and 66.4% for deferoxamine. The relative efficacy of EXJADE to deferoxamine cannot be determined from this study.

In patients who had an LIC at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with EXJADE and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin were observed with EXJADE doses of 20 to 30 mg/kg. EXJADE doses below 20 mg/kg/day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg/kg/day is recommended. (See DOSAGE AND ADMINISTRATION).

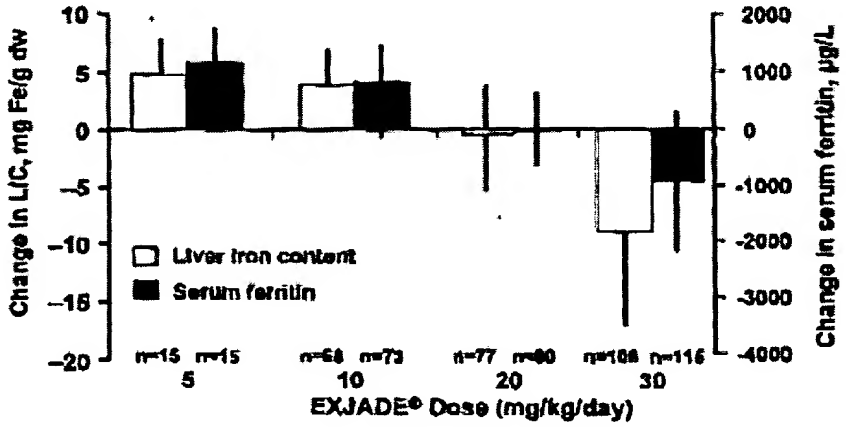


Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following Exjade (5 to 30 mg/kg per day) in Study 1

Study 2 was an open-label, non-comparative trial of efficacy and safety of EXJADE given for 1 year to patients with chronic anemias and transfusional hemosiderosis. Similar to Study 1, patients received 5, 10, 20, or 30 mg/kg per day of EXJADE based on baseline LIC.

A total of 184 patients were treated in this study: 85 patients with β-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n=47; Diamond-Blackfan syndrome, n=30; other, n=22). Nineteen percent of patients were <16 years of age and 16% were ≥ 65 years of age. There was a reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).

Study 3 assessed the safety of EXJADE in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to EXJADE at doses of 5, 10, 20, or 30 mg/kg per day or subcutaneous deferoxamine at doses of 20-60 mg/kg per day for 5 days per week according to baseline LIC. See ADVERSE REACTIONS section for safety experience with EXJADE in patients with sickle cell disease.

INDICATIONS AND USAGE

EXJADE® (deferasirox) is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

CONTRAINDICATIONS

Use of EXJADE® (deferasirox) is contraindicated in patients with hypersensitivity to deferasirox or to any other component of EXJADE.

WARNINGS

Renal

EXJADE-treated patients experienced dose-dependant increases in serum creatinine. These increases occurred at a greater frequency compared to deferoxamine-treated patients (38% vs 15%, respectively) in Study 1. Most of the creatinine elevations remained within the normal range. Serum creatinine should be assessed before initiating therapy and should be monitored monthly thereafter. Dose reduction, interruption, or discontinuation should be considered for elevations in serum creatinine. In the clinical trials, for increases of serum creatinine on two consecutive measures (>33% in patients >15 years of age or >33% and greater than the age-appropriate upper limit of normal in patients <15 years of age), the daily dose of EXJADE was reduced by 10 mg/kg. Patients with serum creatinine above the upper limit of normal were excluded from clinical trials.

In clinical trials, urine protein was measured monthly. Intermittent proteinuria (urine protein/creatinine ratio > 0.6 mg/mg) occurred in 18.6% of EXJADE-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1. Although no patients were discontinued from EXJADE in clinical trials up to 1 year due to proteinuria, close monitoring is recommended. The mechanism and clinical significance of the proteinuria are uncertain.

Hepatic

In Study 1, four patients discontinued EXJADE because of hepatic abnormalities (drug-induced hepatitis in 2 patients and increased serum transaminases in 2 additional patients). Liver function tests should be monitored monthly during EXJADE treatment and dose modifications considered for severe or persistent elevations.

Special Senses

Auditory disturbances (high frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) have been reported at a frequency of <1% with EXJADE therapy in the clinical trials. Auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) are recommended before the start of EXJADE treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, dose reduction or interruption should be considered.

PRECAUTIONS

General

Skin rashes may occur during EXJADE® (deferasirox) treatment. For rashes of mild to moderate severity, EXJADE may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, EXJADE may be interrupted. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration.

Information for Patients

EXJADE should be taken once daily on an empty stomach at least 30 minutes prior to food preferably at the same time every day. The tablets should not be chewed or swallowed whole. The tablets should first be completely dispersed in water, orange juice, or apple juice, and the resulting suspension drunk immediately. After swallowing the suspension any residue should be resuspended in a small volume of the liquid and swallowed.

Patients should be cautioned not to take aluminum-containing antacids and EXJADE simultaneously.

Because auditory and ocular disturbances have been reported with EXJADE, patients should have auditory and ophthalmic testing before starting EXJADE treatment and thereafter at regular intervals. (See WARNINGS, Special Senses).

Patients experiencing dizziness should exercise caution when driving or operating machinery (See ADVERSE REACTIONS).

Laboratory Tests

Serum ferritin should be measured monthly to assess response to therapy and to evaluate for the possibility of overchelation of iron. If the serum ferritin falls consistently below 500 mcg/L, consideration should be given to temporarily interrupting therapy with EXJADE (See DOSAGE and ADMINISTRATION).

In the clinical studies, the correlation coefficient between the serum ferritin and LIC was 0.63. Therefore, changes in serum ferritin levels may not always reliably reflect changes in LIC.

Laboratory monitoring of renal and hepatic function should be performed (See WARNINGS).

Drug Interactions

The concomitant administration of EXJADE and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, EXJADE should not be taken with aluminum-containing antacid preparations.

In healthy volunteers, EXJADE had no effect on the pharmacokinetics of digoxin. The effect of digoxin on EXJADE pharmacokinetics has not been studied.

The concomitant administration of EXJADE and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg were allowed in clinical studies without negative consequences.

The interaction of EXJADE with hydroxyurea has not been formally studied. No inhibition of deferasirox metabolism by hydroxyurea is expected based on the results of an *in vitro* study.

EXJADE should not be combined with other iron chelator therapies as safety of such combinations has not been established.

Drug/Food Interactions

The bioavailability (AUC) of deferasirox was variably increased when taken with a meal. Deferasirox should be taken on an empty stomach 30 minutes before eating.

EXJADE tablets for oral suspension can be dispersed in water, orange juice, or apple juice.

Carcinogenicity/Mutagenesis/Impairment of Fertility

A 104-week oral carcinogenicity study in Wistar rats showed no evidence of carcinogenicity from deferasirox at doses up to 60 mg/kg per day (about 0.48 times the recommended human oral dose based on body surface area). A 26-week oral carcinogenicity study in p53 (+/-) transgenic mice has shown no evidence of carcinogenicity from deferasirox at doses up to 200 mg/kg per day (about 0.81 times the recommended human oral dose based on body surface area) in males and 300 mg/kg per day (about 1.21 times the recommended human oral dose based on body surface area) in females.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was positive in 1 of 3 *in vivo* oral rat micronucleus tests.

Deferasirox at oral doses up to 75 mg/kg per day (about 0.6 times the recommended human oral dose based on body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

Pregnancy, Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in pregnant rats at oral doses up to 100 mg/kg per day (about 0.8 times the recommended human oral dose based on body surface area) and in pregnant rabbits at oral doses up to 50 mg/kg per day (about 0.8 times the recommended human oral dose based on body surface area). These studies have revealed no evidence of impaired fertility or harm to the fetus due to deferasirox. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, deferasirox should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether deferasirox is excreted in human milk. Deferasirox and its metabolites were excreted in breast milk of rats following a 10 mg/kg dose (about 0.08 times the recommended human oral dose based on body surface area). Because many drugs are excreted in human milk, caution should be exercised when deferasirox is administered to a nursing woman.

Pediatric Use

Of the 700 patients who received EXJADE during clinical trials, 292 were pediatric patients 2 to <16 years of age with various congenital and acquired anemias, including 52 patients age 2 to <6 years, 121 patients age 6 to <12 years and 119 patients age 12 to < 16 years. Seventy percent of these patients had β-thalassemia. Children between the ages of 2 to <6 years have a systemic exposure to EXJADE

approximately 50% of that of adults (See CLINICAL PHARMACOLOGY). However, the safety and efficacy of EXJADE in pediatric patients was similar to that of adult patients, and younger pediatric patients responded similarly to older pediatric patients. The recommended starting dose and dosing modification are the same for children and adults. (See CLINICAL STUDIES, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

During the 1 year study, the growth and development were within normal limits.

Geriatric Use

EXJADE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Thirty patients ≥65 years of age were included in clinical trials of EXJADE. The majority of these patients had myelodysplastic syndrome (MDS, n=27; other anemias, n=3). In general, caution should be used in elderly patients due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

A total of 700 patients were treated with EXJADE® (deferasirox) in therapeutic studies lasting for 48 weeks in adult and pediatric patients. These 700 patients included 469 with β-thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 45% were male, 70% were Caucasian and 292 patients were <16 years of age. In the sickle cell disease population, 89% of patients were Black. Four hundred sixty nine (403 β-thalassemia and 66 rare anemias) were entered into extensions of the original clinical protocols. In ongoing extension studies median durations of treatment were 85 to 143 weeks.

The most frequently occurring adverse events in the therapeutic trials of EXJADE were diarrhea, vomiting, nausea, headache, abdominal pain, pyrexia, cough, and an increase in serum creatinine. Gastrointestinal symptoms, increases in serum creatinine and skin rash were dose related.

Table 1 displays adverse events occurring in >5% of patients in either treatment group in Study 1. Abdominal pain, nausea, vomiting, diarrhea and skin rashes were the most frequent adverse events reported with a suspected relationship to EXJADE.

Table 1 Adverse Events Occurring in >5% of β-Thalassemia Patients in Study 1

Preferred Term	EXJADE N=296 n (%)	Deferoxamine N=290 n (%)
Pyrexia	56 (18.9)	69 (23.8)
Headache	47 (15.9)	59 (20.3)
Abdominal pain	41 (13.9)	28 (9.7)
Cough	41 (13.9)	55 (19.0)
Nasopharyngitis	39 (13.2)	42 (14.5)
Diarrhea	35 (11.8)	21 (7.2)
Creatinine increased*	33 (11.1)	0 (0)
Influenza	32 (10.8)	29 (10.0)
Nausea	31 (10.5)	14 (4.8)
Pharyngolaryngeal pain	31 (10.5)	43 (14.8)
Vomiting	30 (10.1)	28 (9.7)
Respiratory tract infection	28 (9.5)	23 (7.9)
Bronchitis	27 (9.1)	32 (11.0)
Rash	25 (8.4)	9 (3.1)
Abdominal pain upper	23 (7.8)	15 (5.2)
Pharyngitis	23 (7.8)	30 (10.3)
Arthralgia	22 (7.4)	14 (4.8)
Acute tonsillitis	19 (6.4)	15 (5.2)
Fatigue	18 (6.1)	14 (4.8)
Rhinitis	18 (6.1)	22 (7.6)
Back pain	17 (5.7)	32 (11.0)
Ear infection	16 (5.4)	7 (2.4)
Urticaria	11 (3.7)	17 (5.9)

*includes 'blood creatinine increased' and 'blood creatinine abnormal' which were reported as adverse events. Also see Table 2

In Study 1, 113 patients treated with EXJADE had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2). Twenty-five patients required dose reductions. Increases in serum creatinine appeared to be dose related (See WARNINGS, Renal). Seventeen patients developed elevations in SGPT/ALT levels > 5 times the ULN at 2 consecutive visits. Two patients had liver biopsy proven drug-induced hepatitis and both discontinued EXJADE therapy (See WARNINGS, Hepatic). Two additional patients, who did not have elevations in SGPT/ALT > 5 times the ULN, discontinued EXJADE because of increased SGPT/ALT. Increases in transaminases did not appear to be dose related.

Table 2 Number (%) of patients with increases in serum creatinine or SGPT/ALT in Study 1

Laboratory parameter	EXJADE N=296 n (%)	Deferoxamine N=290 n (%)
Serum creatinine		
Creatinine > 33% and <ULN at ≥2 consecutive post-baseline visits	113 (38.2)	41 (14.1)
Creatinine increase > 33% and >ULN at ≥2 consecutive post-baseline visits	7 (2.4)	1 (0.3)
SGPT/ALT		
SGPT/ALT >5 x ULN at ≥2 post-baseline visits	25 (8.4)	7 (2.4)
SGPT/ALT >5 x ULN at ≥2 consecutive post-baseline visits	17 (5.7)	5 (1.7)

Adverse events that led to discontinuations included abnormal liver function tests (2 patients) and drug-induced hepatitis (2 patients), skin rash, glycosuria/proteinuria, Henoch Schönlein purpura, hyperactivity/insomnia, drug fever, and cataract (1 patient each).

In the overall population of 700 patients, uncommon adverse reactions (0.1 to 1%) included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue, pharyngolaryngeal pain, early cataract and hearing loss (see PRECAUTIONS). Adverse events which most frequently led to dose interruption or dose adjustment were rash, gastrointestinal disorders, infections, increased serum creatinine, and increased serum transaminases.

OVERDOSAGE

There have been no reports of acute overdose with EXJADE® (deferasirox). Single doses up to 80 mg/kg in iron overloaded β-thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy volunteers, single doses of up to 40 mg/kg were tolerated. There is no specific antidote for EXJADE. In case of overdose, induce vomiting and gastric lavage.

DOSAGE AND ADMINISTRATION

It is recommended that therapy with EXJADE be started when a patient has evidence of chronic iron overload, such as the transfusion of approximately 100 mL/kg of packed red blood cells (approximately 20 units for a 40 kg patient) and a serum ferritin consistently > 1000 mcg/L.

Starting Dose

The recommended initial daily dose of EXJADE is 20 mg/kg body weight.

Maintenance

After commencing initial therapy, it is recommended that serum ferritin be monitored every month and the dose of EXJADE adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 or 10 mg/kg and should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). If the serum ferritin falls consistently below 500 mcg/L, consideration should be given to temporarily interrupting therapy with EXJADE. Doses of EXJADE should not exceed 30 mg/kg per day since there is limited experience with doses above this level.

Administration Instructions

EXJADE should be taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Tablets should not be chewed or swallowed whole. EXJADE should not be taken with aluminum-containing antacid products. Doses (mg/kg) should be calculated to the nearest whole tablet. Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Doses of < 1 g should be dispersed in 3.5 ounces of liquid and doses of > 1 g in 7.0 ounces of liquid. After swallowing the suspension, any residue should be resuspended in a small volume of liquid and swallowed.

HOW SUPPLIED

EXJADE® (deferasirox) Tablets for Oral Suspension

125 mg

Off-white, round, flat tablet with beveled edge and imprinted with "IA" on one side and "NVR" on the other.

Bottles of 30 tablets (NDC 0078-0468-15)

250 mg

Off-white, round, flat tablet with beveled edge and imprinted with "IB" on one side and "NVR" on the other.

Bottles of 30 tablets (NDC 0078-0469-15)

500 mg

Off-white, round, flat tablet with beveled edge and imprinted with "IC" on one side and "NVR" on the other.

Bottles of 30 tablets (NDC 0078-0470-15)

Storage

Store at 25°C (77°F). Excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature]. Protect from moisture.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

NOVEMBER 2005

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
11/2/2005 05:14:19 PM

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450

Dolores DeCarmine — Dolores DeCarmine — 5/22/03

Type or print name — Signature — Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE ISSUED PATENT 6,465,504 OF

RENE LATTMANN ET AL

ISSUED: OCTOBER 15, 2002

APPLICATION NO.: 09/699,765

FILED: OCTOBER 30, 2000

FOR: SUBSTITUTED 3,5-DIPHENYL-1,2,4-TRIAZOLES AND THEIR USE AS PHARMACEUTICAL METAL CHELATORS

ATTENTION: CERTIFICATE OF CORRECTION BRANCH

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER CFR § 1.322

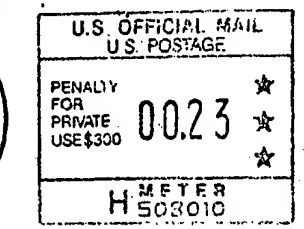
Sir:

Pursuant to 37 CFR 1.322, it is hereby respectfully requested that a Certificate of Correction be issued for United States Patent 6,465,504 containing the corrections set forth on the appended Form PTO 1050.

On the title page, in item (75), the **Inventors'** information was incorrect. The country where the two inventors reside **should be Switzerland and not Sweden**. Also, in item (30), the **"Foreign Application Priority Data"** listed the country where the application was filed incorrectly. The country is also **Switzerland**. Note that the attached copy of the Declaration clearly shows this to be true.

Each of the other errors is believed to be attributable to the Patent and Trademark Office as is evident as shown in the table on page 2:

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231



A request for a Certificate of Correction has been received for U.S. Patent 6465504

4-20918B

JOSEPH J. BOROVIAN
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA, BUILDING 430
EAST HANOVER, NJ 07936-1080

07

Case No. 4-20918B/N1
Application No. 09/699,765
Mailing Date: 5/22/03
Due Date:

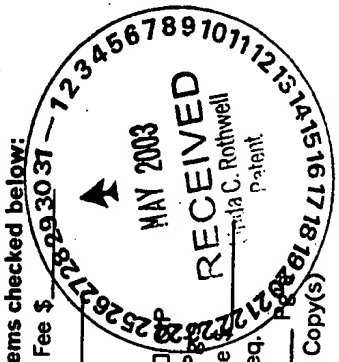
Express Mail No.:

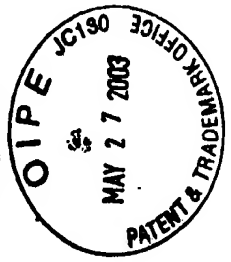
The Patent & Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below:

- ☐ Amendment/Response/Letter - Fee $
- ☐ Appln. Filing Papers - Fee $
  - ☐ PCT National Stage
  - ☐ Provisional Application
  - ☐ RCE ☐ DIV ☐ CONT ☐
  - ☐ Specification ____ Pg's
  - ☐ Executed/Unexecuted Decl. - Fee
  - ☐ Missing Parts/Missing Req.
- ☐ Preliminary Amendment ____ Pg's
- ☐ Claim of Priority ☐ Certified Copy(s)
- ☐ Amendment After Final
- ☐ Notice of Appeal - Fee $
- ☐ Appeal Brief - Fee $
- ☐ Issue Fee Payment $
- ☐ Assignment Rec. Req. - Fee $
- ☐ Formal Drawings ____ Pg's
- ☐ IDS ____ Pg's - Fee $
- ☐ PTO-1449 Form ____ Pg's
- ☐ Pet. for Ext. of Time - Fee $
- ☐ Application Data Sheet
- ☐ Seq. Listings ____ Pg's/Seq. Disk

Response to Request for Certificate of Correction - Request for Certificate of Correction; Form PTO-1058 (2) Encl. Declaration and pp. 11, 24, 25, 26, 27, 31 of Spec.

Initials





82972/99A Rev.1

Location and/or Error in Printed Patent	Location of Support in *Specification or **Amendment
Column 7, line 63, replacement of "alkoXY" with alkoxy"	*Page 11, line 11 beneath the structural formula
Column 8, line 10, replacement of "I" with "II"	*Page 11, line 18 beneath the structural formula
Column 16, last line, replacement of "1.7 9" with "1.7 g"	*Page 24, third line of Example 18
Column 17, line 17, replacement of "tazole" with "triazole"	*Page 24, fifth line of Example 19
Column 17, line 58, replacement of "268-269-269° C." with "268-269° C."	Page 25, sixth line of Example 21
Column 18, line 24, replacement of "13,5" with "[3,5"	*Page 26, second line of Example 24
Column 19, line 34, replacement of "ace" with "acetamide"	*Page 27, seventh line of Example 29
Column 19, line 42, replacement of "l.09" with "1.0 g"	*Page 27, third line of Example 30
Column 19, line 53, after "4.9 (s,2H)", insertion of "7.0 (m, 4H)" and replacement of "7.4 (m,3H)" with "7.4 (m, 3H)"	*Page 28, line 3 and 4

Enclosed are copies of pages 11, 24, 25, 26, 27 and 28, which clearly show the location of support.

Attached is a duplicate of Form PTO 1050, with at least one copy being suitable for printing.

Since the above errors are not ascribable to the patentees, no fee is believed to be necessitated by this Request for Certificate of Correction. However, in the event that a fee is required, the Commissioner is hereby authorized to charge said fee to Deposit Account No. 19-0134 in the name of Novartis.

Please send the Certificate of Correction to the address currently associated with Customer No. 001095, viz:

Thomas Hoxie
Novartis
Corporate Intellectual Property
One Health Plaza – Building 430
East Hanover, NJ 07936-1080

Respectfully submitted,

Joseph J. Borovian
Agent for Patentees
Reg. No.26,631

Novartis
Corporate Intellectual Property.
One Health Plaza – Building 430
East Hanover, NJ 07936-1080
(862)778-7801
JJB/dd
Encls.: Form PTO 1050 (2)
copy of Declaration
copies of pages 11, 24, 25, 26, 27 and 28
postcard
Date: May 22, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 6,465,504 B1
DATED: : OCTOBER 15, 2002
INVENTOR(S) : RENE LATTMANN ET AL

It is certified that there are errors in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page

Item (75) should read:
-- (75) Inventors: **René Lattmann**, Binningen; **Pierre Acklin**, Basel, both of (CH) --.

Item (30) should read:
-- (30) **Foreign Application Priority Data**
Jun. 25, 1996 (CH) .....1593/96 --.

Column 7

Line 63 should read:
-- alkyl, halo-lower alkyl, lower alkoxy or nitrile; R_6 and --.

Column 8

Line 10 should read:
-- formula II in which --.

MAILING ADDRESS OF SENDER:
Joseph J. Borovian
Novartis
Corporate Intellectual Property
One Health Plaza, Building 430
East Hanover, NJ 07936-1080
(862) 778-7801

PATENT NO. 6,465,504 B1

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 6,465,504 B1
DATED: : OCTOBER 15, 2002
INVENTOR(S) : RENE LATTMANN ET AL

It is certified that there are errors in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16

Last line should read:
-- [1,3]oxazin-4-one are boiled under reflux for 5 h with 1.7 g --.

Column 17

Line 17 should read:
-- dimethylaminobenzyl)-IH-[1,2,4]triazole remains as colorless --.

Line 58 should read:
-- remains as colorless crystals of m.p. 268-269° C. --.

Column 18

Line 24 should read:
--2.0 g of ethyl [3,5-bis(2-hydroxyphenyl)-[1,2,4]triazol- --.

MAILING ADDRESS OF SENDER:
Joseph J. Borovian
Novartis
Corporate Intellectual Property
One Health Plaza, Building 430
East Hanover, NJ 07936-1080
(862) 778-7801

PATENT NO. 6,465,504 B1

FORM PTO-1050

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : 6,465,504 B1
DATED: : OCTOBER 15, 2002
INVENTOR(S) : RENE LATTMANN ET AL

It is certified that there are errors in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 19

Line 34 should read:
-- ethoxy)ethyl]acetamide remains as colorless crystals of m.p --.

Line 42 should read:
-- yl]acetate (Example2) and 1.0 g of N,N-bis(2-hydroxyethyl) --.

Line 53 should read:
-- 2H), 4.9 (s, 2H), 7.0 (m, 4H), 7.4 (m, 3H), 7.95 (d, 1H), 8.1 (t, 1H), 11.0 --.

MAILING ADDRESS OF SENDER:
Joseph J. Borovian
Novartis
Corporate Intellectual Property
One Health Plaza, Building 430
East Hanover, NJ 07936-1080
(862) 778-7801

PATENT NO. 6,465,504 B1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 12 -9

IND 58,554

Novartis Pharmaceuticals Corporation
Attention: Ms. Eileen A. Ryan
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Ms. Ryan:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 58,554

Sponsor: Novartis Pharmaceuticals Corporation

Name of Drug: ICL 670 Dispersible Tablets

Date of Submission: June 30, 1999

Date of Receipt: July 1, 1999

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before July 31, 1999, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7310.

Sincerely yours,

Alice Kacuba

Alice Kacuba, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

June 30, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

ICL 670 Dispersible Tablets

INVESTIGATIONAL NEW DRUG APPLICATION

Serial No. 000

Dear Sir or Madam:

In accordance with 21 CFR §312.23, attached is our investigational New Drug Application (FDA Form 1571) and supporting documents for the following investigational compound:

ICL 670 Dispersible Tablets

Indication: Iron Chelation

I wish to bring to your attention that Section 6 includes two protocols each with a question directed to the FDA reviewer (s). The protocols are:

1) **Protocol CICL 670 0103** entitled **"Open metabolic iron balance study with three single oral doses of ICL670A in patients with transfusion–dependent ß-thalassemia"** and **Amendment #1 to CICL 670 0103.**

   It is our intention to initiate this protocol after the 30 day review clock expires. Also included is Amendment No 1 which provides for the inclusion of adolescents over the age of 14 years in Protocol **CICL 670 0103.** A justification for this amendment is also included in Section VI and a question to the FDA relative to Amendment No: 1 is provided.

2) **Draft protocol CICL670 0102:** entitled **"Double-blind, placebo-controlled time-lagged, parallel group study to evaluate the safety and tolerability of ascending multiple oral doses of ICL670A administered to patients with transfusion-dependent ß-thalassemia"**.

   The sponsor has provided this protocol for FDA comment. This protocol represents the first multi-dose trial and is expected to begin in September. Provided with this protocol is a question for the FDA reviewer relative to the dose selection. Also because this study is a multi dose study an ophthalmic assessment is included on a finding of cataracts in a repeat dose rat toxicology study.

We respectfully request your review of Protocol CICL 0103 and Amendment No. 1 within the 30 day review period.

A response to our question on Protocol CICL 0102 would be appreciated by August so the trial may initiate in September.

This IND application and all subsequent amendments thereto are confidential and their contents are not to be disclosed without the express written consent of Novartis Pharmaceuticals Corporation.

If you have any questions or comments, please contact me at (973) 781-7661.

Sincerely,

Eileen A Ryan
Associate Director
Drug Regulatory Affairs

/cs
Attachments
Submitted in triplicate

990630cs.doc

APPENDIX G

Chronology of significant regulatory activities between Applicant and FDA during the IND and NDA periods:

IND PERIOD

06/30/1999	Submitted an Investigation New Drug Application for ICL670 Dispersible Tablets – Indication: Iron Chelation. Two protocols are included, each with a question directed to the FDA reviewer (protocol CICL 670 0103 with Amendment No. 1 and draft protocol CICL670 0102).
07/12/1999	FDA LETTER acknowledging receipt on July 1, 1999 of the original IND dated June 30, 1999. Assigned IND No. 58,554.
07/22/1999	Telecon with FDA to discuss three recommendations for changes to Protocol 0103 submitted in the original IND.
07/22/1999	Fax to FDA providing Novartis' commitment to amend the clinical study protocol 0103 as recommended by FDA, discussed at telecon of even date.
07/27/1999	Fax to FDA clarifying the trial design description that appeared in protocol 0103 in response to the Agency's recent request.
08/04/1999	A corrected Form FDA 1572 was submitted to reflect changes to box 14.
08/04/1999	Official copies of the faxes dated July 22 and 27, 1999 are submitted.

08/19/1999	FDA LETTER referencing the agreement reached at the July 22, 1999 teleconference revising protocols 0103 and 0102 as well as requesting additional revision to same protocols. CMC issues to be addressed as the drug development proceeds are also listed.
10/06/1999	New protocol CICL670 0104 (replaces 0103 and 0102 and incorporates all suggested changes from the Division) entitled: "Randomized, double-blind, placebo controlled, time-lagged, parallel-group study to evaluate the iron balance, safety and tolerability of multiple oral doses of ICL670A in patients with transfusion dependent beta-thalassemia". A revised investigator's Brochure is also included.
10/12/1999	Fax to FDA in response to a request from the Pharm/Tox reviewer for information on Klucel HF.
10/14/1999	This submission supersedes Serial No. 003. A complete 004 copy of all material (with the corrected protocol CICL670 0104) previously sent is included. Initiation of this proposed study is planned for the second week of November and Novartis is asking the Division for any comments on or before November 1, 1999.
11/22/1999	FDA letter containing comments and recommendations from the review of the clinical protocol 0104 submitted on October 14, 1999, Serial No. 004
03/09/2000	This submission contains a full response to all CMC issues contained in the Agency's letter dated August 19, 1999.
05/02/2000	New investigator to Study No. CICL670A 0104: Patricia Giardina, MD.
06/07/2000	Amendment No. 1 to Study No. ICL670A 0104.
07/27/2000	Amendment No. 2 to Study No. ICL670A 0104.
11/06/2000	Annual Report covering the period of July 1, 1999 through June 30, 2000. Includes preclinical and clinical study information and CMC changes.

11/06/2000	Amendment No. 3 to Study No. 0104.
01/09/2001	This amendment contains updated stability data for both the drug substance and drug product.
01/15/2001	Amendment No. 4 to Study No. 0104.
03/23/2001	Final Report for Study No. 0101 entitled "A double-blind, placebo-controlled, tolerability, safety and pharmacokinetic study with ascending single oral doses of ICL670A administered in a sequential order to patients with transfusion-dependent beta-thalassemia."
04/17/2001	This correspondence requests a special protocol assessment on the two carcinogenicity protocols being submitted to determine whether the Division is in agreement with this study program as adequate to assess the risk for patients.
04/25/2001	FDA letter stating that the April 17, 2001, request for a special protocol assessment will not be accepted. The protocols are to be resubmitted as separate submissions and for the rat carcinogenicity study protocol, a copy of the full report from the 26-week toxicology study in rats is to be included.
04/30/2001	In response to an FDA letter dated April 25, 2001 concerning Novartis' April 17, 2001 request for special protocol assessment, this correspondence contains the resubmission of the rat carcinogenicity study protocol and a copy of the full report from the 26-week rat toxicology report.
04/30/2001	In reference to the request for special protocol assessment (Serial No. 016) on the rat carcinogenicity study protocol, this submission contains additional information to clarify questions discussed by telephone.
06/07/2001	Fax from FDA containing the final CAC report in response to Carcinogenicity Special Protocol Assessment Request, Serial No. 016, April 30, 2001.

06/19/2001	FDA letter containing comments and recommendations on the Request for Special Protocol Assessment amendments, Serial No. 16 and 17 (RAT CAR study protocol).
07/06/2001	In response to an FDA letter dated April 25, 2001, concerning Novartis' April 17, 2001, request for Special Protocol Assessment, this correspondence contains the draft mouse carcinogenicity protocol for review.
07/09/2001	This submission provides comments in response to an FDA letter dated June 19, 2001, regarding the 104-week carcinogenicity study in rats.
07/17/2001	FDA letter stating that the submission dated July 6, 2001, Serial No. 017, (special carcinogenicity protocol assessment) is under review and a written response will be coming within 45 days of its receipt.
08/21/2001	Fax from FDA containing the final CAC report in response to the Mouse Carcinogenicity Special Protocol Assessment Report.
08/31/2001	FDA letter containing comments and recommendations in response to a special carcinogenicity protocol assessment dated July 6, 2001, Serial No. 017.
10/26/2001	Eric Nisbet-Brown, MD; Protocol No. CICL670 0104; rash maculo-papular.
11/30/2001	This amendment contains updated documentation in support of minor changes to the drug substance manufacturing process.
12/20/2001	Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, body temperature increased, fatigue, pruritus NOS.
12/20/2001	Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, pruritus NOS.

01/04/2002	Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, body temperature increased, fatigue, transaminases increased, pruritus NOS; follow-up.
01/15/2002	Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, body temperature increased, fatigue, transaminases increased, pruritus NOS; follow-up.
01/17/2002	Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, blood in stool, pruritus NOS; follow-up.
02/05/2002	FDA letter requesting an Annual Report or a request to withdraw IND.
02/14/2002	Request for an end of Phase II meeting to discuss the registration program.
02/25/2002	Patricia Giardina, MD; Protocol No. ICL670 0104; urticaria acute, blood in stool, pruritus NOS; follow-up.
02/26/2002	Fax from FDA containing information on the meeting to be held on April 9, 2002.
03/12/2002	This Briefing Book is being submitted in preparation for the End of Phase II Meeting scheduled for April 9, 2002.
03/27/2002	Annual Report covers the period of July 1, 2000, through June 30, 2001. Includes preclinical and clinical information, CMC changes and a revised investigator's Brochure dated May 7, 2001.
04/05/2002	Fax to FDA containing the final list of Novartis attendees for the End of Phase II Meeting on April 9, 2002.
04/09/2002	Fax from FDA containing the April 9, 2002, meeting roster and a copy of the responses passed out at the meeting to all attendees.
04/10/2002	This submission contains copies of overheads presented by Novartis at the End-of-Phase II meeting.

06/03/2002	FDA letter containing the minutes of the April 9, 2002, End of phase 2 meeting.
08/08/2002	In response to an FDA letter dated August 31, 2001, concerning Novartis' July 7, 2001 Request for Special Protocol Assessment, this correspondence contains the revised draft mouse carcinogenicity protocol for review.
08/22/2002	FDA letter indicating that the request, Serial No 003, for a special carcinogenicity protocol assessment is being reviewed.
09/19/2002	Fax from FDA containing the final CAC report in response to the Carcinogencity Special Protocol Assessment request.
10/07/2002	FDA Letter containing comments on recommendations on the amendment dated August 8, 2002 (Serial No. 033) which requested a special mouse carcinogenicity protocol assessment.
10/21/2002	Annual Report covering the period of July 1, 2001, through June 30, 2002. Includes preclinical and clinical study/safety information.
10/23/2002	In reference to the final CAC report for the proposed 26 week oral, mouse carcinogenicity study, this correspondence contains responses to the CAC recommendations and conclusions and asks for the Division's concurrence before the study proceeds.
11/14/2002	Fax from FDA containing the final CAC report in response to the Carcinogenicity Special Protocol Assessment request.
11/18/2002	Submission containing a request for a special protocol assessment for Protocol No. CICL670A0107 entitled, "A randomized, comparative, open label phase III trial on efficacy and safety of long-term treatment with ICL670 (5 to 40 mg/kg/day) in comparison with deferoxamine (20 to 60 mg/kg/day) in beta-thalassemia patients with transfusional hemosiderosis."

11/18/2002	Submission containing a request for a special protocol assessment for Protocol No. CICL670A0108 entitled, "A multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL670 (5 to 40 mg/kg/day) given for at least 1 year to patients with chronic anemias and transfusional hemosiderosis unable to be treated with deferoxamine."
12/03/2002	FDA Letter containing comments and recommendations on the October 23, 2002 (Serial No. 035) request for a special carcinogencity protocol assessment.
12/05/2002	Correspondence to the Division in reference to requests for special protocol assessment and a letter received from the Office of Orphan Products Development which notified Novartis that deferasirox qualifies for orphan-drug designation.
12/13/2002	In reference to the End-of-Phase 2 meeting held on April 9, 2002, this correspondence requests a Special Protocol Assessment for Protocol No. CICL670A0109 entitled, "An open label, phase II study to evaluate the safety, tolerability, pharmokinetics and the effects on liver iron concentration of repeated doses of 10 mg/kg/day of ICL670 administered to sickle cell disease in patients with transfusional hemosiderosis."
12/20/2002	In reference to FDA's recommendation during the End of Phase II meeting held on April 9, 2002, this submission contains an application for Fast Track Designation.
01/03/2003	FDA letter containing responses to questions submitted in the request for a special clinical protocol assessment (Serial No. 36).
01/03/2003	FDA letter containing responses to questions submitted in the request for a special clinical protocol assessment (Serial No. 37).
01/15/2003	FDA letter notifying Novartis that the submission (Serial No. 039), that requested a special protocol assessment, is being reviewed.

01/20/2003	In reference to January 3, 2003, FDA special protocol assessment, this correspondence requests clarification on two points raised.
01/21/2003	This amendment contains a stability protocol for review.
01/30/2003	FDA letter containing responses to questions submitted in the request for a special clinical protocol assessment (Serial No. 39).
02/19/2003	This correspondence notifies FDA of a possible data manipulation that occurred at Covance Laboratories, Geneva, Switzerland.
02/19/2003	This correspondence response to issues raised in the January 3 and 30, 2003, FDA Special Protocol Assessment for protocols CICL670A0107, CICL670A0108, and CICL670A0109.
02/21/2003	FDA letter stating that the December 20, 2002 request for fast track designation has been granted.
03/19/2003	A Proposed Pediatric Study request is submitted for the treatment of patients with sickle cell anemia (Protocol No. CICL670A0110).
03/24/2003	Request for FDA review of the proposed proprietary name: Exjade.
03/26/2003	Teleconference with FDA to discuss the review status of the proposed stability protocol submitted January 21, 2003.
04/04/2003	Amendment providing for minor specifications to the drug substance and two new dosage strengths: 150mg tablets/KN3766078 and 500 mg tablets/KN3756087.
04/23/2003	Request for teleconference to discuss the clarification points raised in the Novartis communication dated January 20, 2003, regarding the Special Protocol Assessment for protocols 0107 and 0108.
04/23/2003	Correspondence responding to an FDA request for additional information concerning the March 24, 2003 submission requesting a review of a proprietary name candidate for ICL670.

05/08/2003	Facsimile from the FDA confirming the teleconference scheduled for June 16, 2003.
05/09/2003	Request for teleconference with Division to discuss options that may bring this product to market significantly earlier for a certain subset of patients who are in most need.
05/19/2003	New Investigator to Study No. CICL670A 0107: Dr. E. Vichinsky; Study No. CICL670 0108: Dr. E. Vichinsky; Study No. CICL670 0109: Dr. B. W. Clowney.
05/22/2003	FDA letter containing comments and recommendations on amendments dated January 20, 2003 (Serial No. 041) and February 19, 2003 (Serial No. 044).
05/22/2003	Briefing material for June 16, 2003, teleconference to discuss the clarification points raised in January 20, 2003 correspondence that remain outstanding.
05/30/2003	In reference to the April 9, 2002, End of Phase II meeting, this submission contains a preclinical protocol, Study No. 0370030, an oral neonatal and juvenile development study in rats for review.
06/02/2003	New Protocol to Study No. 0117 entitled "A protocol to allow treatment with ICL670 for patients with or at risk of life-threatening complications of transfusional iron overload who are unable to tolerate other iron chelators because of documented sever toxicity.
06/05/2003	Submission of toxicology report "An oral neonatal and juvenile development dose range-finding study in rats", Study No. 0370003.
06/09/2003	Correspondence and supporting documentation for the use of Crono 30 infusion pumps in the ongoing clinical trials.
06/10/2003	Correspondence on the resolution of clarification points raised concerning the Special Protocol Assessment.
06/16/2003	Submission of briefing materials for the July 18, 2003 teleconference.

06/24/2003	In reference to the January 3, 2003 FDA Special Protocol Assessment for protocol ICL670A0108, this submission contains Amendment No. 1 to this protocol.
06/24/2003	In reference to the January 3, 2003 FDA Special Protocol Assessment for protocol ICL670A0108, this submission contains Amendment No. 1 to this protocol.
07/01/2003	New investigators to Study No. 0107: Drs. A. Cohen, E. Neufeld; Study No. 0108: Drs. M. Cunningham, M.R. Jeng, A. Cohen, S.D. Rifkin; Study No. 0109: Drs. A. Kutlar, P. Swerdlow.
07/03/2003	This submission contains Amendment No. 1 to the Final Study Report for CICL670A0101 submited March 23, 2001 (Serial No. 013).
07/07/2003	This correspondence responds to an FDA for additional information for the SQUID machines in preparation for the July 18, 2003 teleconference.
07/09/2003	Facsimile from the FDA containing responses to questions listed in the June 16, 2003, package for the July 18, 2003 teleconference.
07/16/2003	Cancellation of teleconference with the Division to discuss regulatory options that may bring this compound earlier to the market.
07/17/2003	New investigators to Study No. 0107: Drs. P.J. Giardina, M.R. Jeng; Study No. 0108: Dr. P.J. Giardina: Study No. 0109: Drs. E. Vichinsky, O.C. Onyekwere; Study No. 0117: Dr. M. Cunningham.
07/18/2003	FDA letter containing issues to be addressed concerning the proposed pediatric study request dated March 19, 2003.
07/30/2003	Amendment No. 2 to Study No. 0109.
08/01/2003	FDA containing comments and recommendations on amendments dated March 9, 2000 (Serial No. 005), January 9, 2001 (Serial No. 011), November 30, 2001.(Serial No. 020) and April 4, 2003 (Serial No. 074).

08/01/2003	FDA letter containing comments and recommendations on the new preclinical protocol, 0370030 dated May 30, 2003 (Serial No. 053) and a preclinical report for Study 0370003 dated June 5, 2003 (Serial No. 055).
08/21/2003	Response to the August 1, 2003, FDA review of toxicology protocol #0370030 submitted May 30, 2003.
08/27/2003	Annual Report covering the period of July 1, 2002 through June 30, 2003. Includes clinical study information, preclinical study information, CMC changes and investigator's brochure.
09/05/2003	This submission response to the CMC questions in reference to the August 1, 2003 FDA letter containing comments and recommendations on amendments dated March 9, 2000 (Serial No. 005), January 9, 2001 (Serial No. 011), November 30, 2001 (Serial No. 020) and April 4, 2003 (Serial No. 074).
09/08/2003	New investigator to Study No. 0107: Dr. A.A. Thompson; Study No. 0109: Dr. F.L. Wilson.
09/16/2003	In reference to the August 1, 2003, FDA review of the neonatal rat toxicology protocol #0370030, this correspondence requests a Type A Meeting to discuss the necessity of conducting a neonatal marmoset toxicology study.
09/24/2003	In reference to the Special Protocol Assessment (SPA) provided by FDA for Study CICL670A0109 on January 30, 2003, this correspondence requests a Type A Meeting to discuss possible amendments to the protocol as solutions for the recruitment issue for this study.
09/30/2003	Facsimile from FDA containing information on the telecom scheduled for October 30, 2003.

09/30/2003	In reference to the September 16, 2003, Type A Meeting request, this submission contains relevant background information regarding the toxicology development program for this compound.
09/30/2003	In reference to the September 16, 2003, Type A Meeting request, this submission contains relevant background information regarding the recruitment issues and possible protocol amendment solution for Study CICL670A0109.
10/07/2003	New investigator to Study No. 0109: Dr. M. Francisco.
10/16/2003	Submission of an addendum to the Briefing Book dated September 30, 2003, in preparation for the October 30, 2003 teleconference to discuss the FDA request to perform a neonatal marmoset study.
10/22/2003	Facsimile from FDA containing their responses to the questions listed in the October 7, 2003 background package for a Type A meeting.
10/23/2003	Facsimile from FDA containing their responses to the questions listed in the October 7, 2003 background package for a Type A meeting.
10/20/2003	New investigator to Study No. 0107: Drs. T. Coates, L. Rice, R. Wise, P. Kelly, A. Adewoye.
10/30/2003	FDA minutes of a teleconference regarding the neonatal marmoset monkey study.
11/20/2003	FDA letter containing minutes of the October 23, 2003 Type A meeting.
11/24/2003	Dr. Alan Cohen; Rash maculo-papular, pyrexia, palpitations, rash erythematous.
12/03/2003	Dr. Alan Cohen; Rash maculo-papular, pyrexia, palpitations, rash erythematous; Follow-up #1.
12/16/2003	Dr. Alan Cohen; Rash maculo-papular, pyrexia, palpitations, rash erythematous; Follow-up #2.

12/19/2003	New Investigator to Study No. 109: Dr. Rita Bellevue.
12/19/2003	FDA letter containing comments and recommendations on the CMC amendment dated September 5, 2003 (Serial No. 070).
12/23/2003	Amendment No. 3 to Study No. 0109.
01/05/2004	FDA letter responding to the request for an evaluation of the tradename "Exjade".
01/05/2004	FDA letter responding to the questions contained in the April 18, 2003 amendment regarding the March 19, 2003 Proposed Pediatric Study Report and the Division's letter denying the PPSR.
01/19/2004	New investigator to Study No. 0109: Drs. K.L. Hassell, S. R. Cataland, W.C. Owen.
01/19/2004	Amendment No. 2 to Study No. 0107. Amendment No. 0108 to Study No. 0108.
02/02/2004	New protocol to Study No. 0107E1 entitled "A 3-year open label, non-comparative extension to a randomized, comparative, open label phase II trial on efficacy and safety of long term treatment with ICL670 (5 to 40 MG/KG/day) in comparison with deferoxamine (20 to 60 MG/KG/day) in B-thalassemia patients with transfusional hemosiderosis; New Protocol to Study No. 0108E1.
02/04/2004	Annual update, November 21, 2002, November 20, 2003, for the Orphan Drug Designation number 02-1610.
03/02/2004	This correspondence informs the Division that Novartis is actively working to obtain additional information regarding the death of a patient (PHHO2004TN02870) reported March 1, 2004.
03/12/2004	New investigator to Study No. 0109: Dr. Julia Margarita Cruz, MD.
03/17/2004	Alan Cohen: headache, illusion, anxiety.

03/18/2004	Facsimile from FDA containing advise on safety reports, SN-103, 104 and 105.
03/23/2004	New protocol 2101 entitled "A single center, open-label two treatment randomized, two period, crossover study to evaluate the absolute bioavailability of a single 375 mg oral dose of ICL670 in the form of tablets compared to 130 mg ICL670 as an intravenous infusion in healthy volunteers". Investigator: K.C. Lasseter, MD. Also included are CMC and toxicology information to support the new dosage form, 90 mg.5ml ICL670 concentrate for solution for intravenous administration.
04/02/2004	Alan Cohen: Headache, illusion, anxiety; Follow-up #1.
04/09/2004	New protocol to Study No. 2102 entitled "A single-center, open label, two treatment randomized, two-period cross-over study to evaluate the effect of a single oral 20 mg/kg dose of ICL670 on the pharmacokinetics of daily 0.25 mg. oral administration of digoxin in healthy volunteers.
04/09/2004	In reference to the October 23, 2003 meeting, this correspondence informs the Division that the clinical development plan for assessing iron overload will be submitted end of May 2004.
05/13/2004	Response to FDA request for information regarding safety reports; Serial No. 103, 104 and 105.
05/18/2004	This letter authorizes the FDA to refer to this IND in support of an IND that will be filed by P. Greenberg, MD.
05/19/2004	Request for a Type A meeting to discuss whether 4-hydrazinobenzoic acid meets the requirements for a starting material.
05/21/2004	Request for a Type A meeting to discuss the juvenile animal model that will provide sufficient information on potential biliary toxicities to support use of ICL670 in children.

05/21/2004	In reference to the Special Protocol Assessment for study CICL670A 0109, this submission requests a Type A meeting to discuss the acceptability of a replacement study design (CICL670A 2201) for the intended sickle cell patient population.
05/24/2004	Facsimile from FDA containing requests for information regarding Serial No. 109 and Serial No. 115.
05/26/2004	New investigator to Study No. 0109: Z. Yasin, MD.
05/27/2004	FDA request for information regarding Serial No. 109 and Serial No. 115
06/02/2004	Submission of additional, corrected copies of Briefing Book submitted May 19, 2004.
06/03/2004	FDA letter stating that the requested meeting concerning a starting material is unnecessary since adequate justification was provided in the May 19, 2004 submission.
06/03/2004	Alan Cohen: Headache, illusion, anxiety; Follow-up #2.
06/07/2004	FDA letter containing details for the type A meeting scheduled for June 28, 2004.
06/08/2004	Amendment No. 1 to Study No. 2102.
06/11/2004	E-mail to FDA containing a list of participants and questions from the Briefing Book for the June 28, 2004 meeting.
06/11/2004	Submission of 2 Briefing Books in preparation for the June 28, 2004 meeting to discuss juvenile toxicology studies and the development program in patients with sickle cell disease and clinical trials on cardiac safety.
06/16/2004	Addendum to Briefing Book for June 28, 2004 meeting.
06/22/2004	This submission contains a revised Investigator's Brochure (Edition 7) and addendum as noted in the submission dated May 13, 2004.

06/24/2004	Facsimile from FDA containing responses to meeting questions listed in the June 11, 2004, background package.
06/25/2004	New Investigator to Study No. 0109; Drs. T. Coates, L. Frankel.
06/29/2004	New Investigator to Study No. 0109; Dr. Liesl Mathias, MD.
06/30/2004	In reference to an agreement reached at the October 23, 2004 meeting to discuss recruitment issues and protocol changes for Study ICL67000109 in patients with sickle cell disease, this submission contains a Briefing Book on methods to assess iron overload.
07/01/2004	This letter authorizes the FDA to refer to this IND to support an IND that will be filed by C. Schiffer, MD.
07/08/2004	New investigator to Study No. 0109; Drs. R. J. Labotka, A. A. Thompson.
07/08/2004	Dr. Patricia Giardina: Klebsiella sepsis, urosepsis, pulmonary hypertension, electrocardiogram abnormal, chest pain, dyspnoea, cardiac murmur, back pain, pyrexia.
07/16/2004	Submission of the final clinical pharmacology report Study No. 0101.
07/26/2004	FDA letter containing a copy of the minutes on June 28, 2004 to discuss issues regarding QTc and the need for non-rodent study.
07/26/2004	FDA letter containing minutes of the minutes on June 28, 2004 to discuss issues regarding QTc and the need for non-rodent study.
07/27/2004	Request for pre-NDA meeting to discuss the content of the submission to support the indication: treatment of chronic iron overload due to repeated blood transfusions.
07/28/2004	New Investigator to Study No. 107E1: Dr. Alan Cohen, MD; Study No. 109: Drs. J. Eckman, P.A. Lane, Jr., L.J. Bengamin, P.J. Giardina, L. Krishnamurti, M. Heeney, J. Kwiatkowski.

08/03/2004	E-mail to FDA regarding the proposed juvenile mouse tox study protocol.
08/03/2004	In reference to the June 28, 2004, meeting with the Division, this correspondence requests a review of the draft juvenile mouse toxicology study protocol.
08/11/2004	FDA letter providing details about the requested (July 27, 2004) pre-NDA meeting scheduled for October 1, 2004.
08/11/2004	Facsimile from FDA containing a pre-NDA granted letter and a request for additional copy of the submission that included information on the SQUID and MRI.
08/16/2004	Clinical report for Study No. 0115 (2 volumes).
08/18/2004	In response to the August 11, 2004 request, this submission contains an additional desk copy of the Briefing Book on methods to assess iron overload submitted June 30, 2004.
08/18/2004	In reference to the June 28, 2004 meeting, this correspondence responds to a request from the Division to review a copy of the full protocol for Study No. CICL670A2122.
08/20/2004	Telecon with FDA regarding the status of the review of preclinical and clinical protocols submitted August 3 and 18, respectively.
08/25/2004	Annual Report covering the period June 29, 2003 through June 30, 2004. Includes clinical study information, preclinical study information and CMC changes.
08/30/2004	New Investigator to Study No. 0108E1: Drs. E. Vichinsky, M. Cunningham.
08/30/2004	New Investigator to Study No. 0107E1: Drs. A. Cohen, E. Neufeld; Study No. 0108E1: Dr. Alan Cohen.

08/31/2004	FDA letter containing comments and recommendations on the final draft protocol in mice submitted August 3, 2004, Serial. No. 157.
08/31/2004	Briefing book submitted in preparation for the October 1, 2004, pre-NDA meeting.
09/15/2004	Dr. Lennette Benjamin: Hypersensitivity, pyrexia, headache, disease progression, oedema peripheral, breast oedema, face oedema.
09/16/2004	E-mail to FDA regarding the moving of the hematologic products to the Oncology Division and the impact on the review.
09/16/2004	Teleconference with FDA regarding the review status of the QT protocol (Study No. 2122).
09/22/2004	Teleconference with FDA regarding orphan drug designation issues for the preNDA meeting scheduled for October 1, 2004.
09/29/2004	FDA letter containing comments on the protocol for Study No. CICL670A2122 submitted August 18, 2004.
09/29/2004	New investigator to Study No. 0107E1: Drs. E.Vichinsky, M.R. Jeng, A.A. Thompson; Study No. 0108E1: Dr. M.R. Jeng; Study No. 0109: Drs. R. Wise, I. Prasannan.
09/29/2004	Amendment No. 3 to Study No. 107 and Study No. 108.
09/30/2004	Facsimile from FDA containing response to the questions listed n the August 31, 2004 background package.
09/30/2004	Dr. Lennette Benjamin: Hypersensitivity, pyrexia, headache, disease progression, oedema peripheral, breast oedema, face oedema; Follow-up #1.
09/30/2004	Dr. Patricia Giardina: Klebsiella sepsis, urosepsis, pulmonary hypertension, electrocardiogram abnormal, back pain, pyrexia, chest pain, dyspnoea, cardiac murmur; Follow-up #1.

10/31/2004	FDA letter containing comments on the protocol revisions for Study No. 0107 submitted August 18, 2004.
10/15/2004	Dr. Spero Cataland: Pancreatitis, cholelithiasis, sickle cell anaemia with crisis, abnormal pain, nausea, vomiting.
10/19/2004	FDA letter containing minutes of the pre-NDA meeting held on October 1, 2004.
10/20/2004	New protocol to Study No. 0109E1 entitled "A one year open label, non-comparative extension to a randomized, multicenter, phase II study to evaluate the safety, tolerability, pharmacokinetics and the effects on liver iron concentration of repeated doses of 5-30 mg/kg/day of ICL670 relative to deferoxiamine in sickle cell disease patients with transfusional hemosiderosis."
10/21/2004	New Investigator to Study No. 0107E1: Dr. Patricia J. Giardina; Study No. 0108E1: Patricia J. Giardina; Study No. 0109 E1: Dr. Onyinye C. Onyekwere.
10/22/2004	Request for a type A meeting to discuss issues that have become apparent since the pre-NDA meeting and to seek guidance and agreement regarding management of their impact.
10/29/2004	Amendment No. 2 to Study No. 0107E1.
11/02/2004	In reference to the FDA letter dated September 29, 2004, this correspondence responds to questions on protocol 2122 (Serial No. 161).
11/02/2004	FDA letter responding to a request for a meeting (Type A) and containing the meeting specifics.
11/04/2004	Submission of background information for the teleconference scheduled for November 10, 2004 to seek FDA's input on the acceptability of an amended definition of the population for primary analysis of non-inferiority in Trial 0107.

11/05/2004	E-mails to/from FDA regarding information to be presented at the November 10, 2004, teleconference.
11/10/2004	Facsimile from FDA containing responses to Novartis' questions regarding Study 0107.
11/10/2004	FDA minutes of a meeting held November 10, 2004, to discuss the proposed amended definition of the population for primary analysis for Trial 0107.
11/12/2004	This correspondence responds to the FDA letter dated October 13, 2004, that contained comments and recommendations on the change in protocol submission for Study No. CICL670A0107.
11/16/2004	Amendment No. 2 to Study No. 0108E1.
11/17/2004	This revised Proposed Pediatric Study Request contains responses to the July 18, 2003 FDA letter.
11/18/2004	New protocol to Study No. 2122 entitled "A randomized, blinded, active placebo controlled, parallel group study to evaluate the cardiac safety of single doses of ICL670 (20 to 40 mg/kg) in healthy volunteers.
11/18/2004	New investigator to Study No. 107E1: Dr. Thomas Coates, MD.
11/18/2004	E-mail to FDA regarding the status of various IND amendments and the CMC section for the NDA under the Pilot 1 guidance.
11/19/2004	Teleconference with FDA to discuss the protocol amendment for Study 109E submitted October 20, 2004, Serial No. 177.
11/22/2004	New protocols: Study No. US02 entitled "An open label, safety and tolerability study of deferasirox for treatment of transfusional iron overload in low-risk and INT-1 myelodysplastic patients." Study No. US03 entitled "An open label, safety and tolerability study of deferasirox for treatment of transfusional iron overload in low-risk and INT-1 myelodysplastic patients using serum ferritin monitoring."

11/30/2004	Submission of a final report for bioavailability Study 2101.
11/30/2004	Submission of additional desk copies of the Proposed Pediatric Study Request submitted November 17, 2004.
12/01/2004	New protocol to Study No. 2201 entitled "A randomized, open-label, multi-center, phase II study to evaluate the safety and efficacy of oral ICL670 (deferasirox) 20 mg/kg/day relative to subcutaneous deferoxamine in sickle cell disease patients with iron overload from repeated blood transfusions.
12/22/2004	Amendment No. 4 to Study No. CICL670A0109.
12/23/2004	Investigator's Brochure (Edition 8, replacing Edition 7 dated 08-Feb-2004).
12/23/2004	New investigator to Study No. 2122: Dr. Jerry M. Herron, MD.
01/04/2005	Amendment No. 3 to Studies Nos. 0107E1 and 0108E1.
01/14/2005	This CMC amendment provides technical documentation in support of the introduction of an additional clinical trial service form "Market Form (MF)".
01/24/2005	Amendment No. 1 to Study No. US02.
01/28/2005	Submission of Clinical Study Report No. 0106.
02/07/2005	Telecon with FDA regarding the revised PPSR submitted November 17,2 004 (Serial No. 186).
02/11/2005	Submission of the final clinical pharmacology study report (Study No. 2120).
03/02/2005	Amendment No. 1 to Study No. 0109E1.
03/14/2005	New investigator to Study No. 0109E1; Drs. E. Vichinsky, L. Rice, P. Kelly, M.F. Gonzalez, W.C. Owen; Study No. 0117: Dr. Patricia J. Giardina, MD.

03/18/2005	New Investigator to Study No. 0109E1: Drs. Richard J. Labotka, MD, Cameron Tebbi, MD.
03/21/2005	Protocol Amendment: After this Protocol was submitted November 24,2004 numerous changes were made which were incorporated into the protocol as a complete revision, rather than an amendment.
03/25/2005	Submission of final clinical reports for studies: A0105, A0105E1, A0105F, A2101, A2102.
03/28/2005	Teleconference with FDA regarding revised PPSR submitted in November.
04/05/2005	FDA letter stating that based on the review of the current (November 17, 2004) proposed pediatric study request, the Division is unable to issue a Written Request.
04/07/2005	Submission of Clinical Study Report No. 0104 (6 volumes).
04/14/2005	Teleconference with FDA regarding the PPSR and upcoming NDA submission.
04/14/2005	Submission of Clinical Study Report No. CICL670A0105E2 (6 volumes).
04/15/2005	Teleconference with FDA regarding PPSR/Written Request.
04/15/2005	Dr. Jacqueline Madden: Lymphadenopathy, sickle cell anaemia with crisis, pyrexia, chills, blood alkaline phosphatase increased, pain, granuloma.
04/19/2005	Teleconference with FDA regarding the Division's letter on the PPSR dated April 5, 2005.
04/20/2005	Teleconference with FDA to discuss the PPSR submitted November 17, 2004 and the non-issuance of a WR.
04/21/2005	Dr. Billy Clowney, MD: Sickle cell anaemia with crisis, disease progression, otitis media, angiopathy, haemolytic anaemia.

04/27/2005	Dr. Billy Clowney, MD: Sickle cell anaemia with crisis, disease progression, otitis media, angiopathy, haemolytic anaemia; Follow-up #1.
04/29/2005	Dr. Zahida Yasin: Pulmonary embolism, lobar pneumia, chest pain, dyspnoea, night sweats, feeling hot.
05/02/2005	New investigator to Study No. 0109E1: Drs. A. Kutlar, J. Cruz, B.W. Clowney, C.D. Scher, S. Cataland, Z. Yasin.
05/05/2005	Dr. Zahida Yasin: Pulmonary embolism, lobar pneumia, night sweats, feeling hot, chest pain, dyspnoea; Follow-up #1.
05/05/2005	Dr. Jacqueline Madden: Tuberculosis, sickle cell anaemia with crisis, lymphadenopathy, pyrexia, chills, blood alkaline phosphatase increased, pain, granuloma; Follow-up #1.
05/05/2005	Dr. Zahida Yasin: Catheter related complication, superior vena caval occlusion, infection, jugular vein distension, face oedema, local swelling, neck pain, dyspnoea, apnoea.
05/12/2005	New Protocol to Study No. 2203 entitled "A study to provide expanded access of EXJADE (deferasirox) to patients with congential disorders of red blood cells and chronic iron overload from blood transfusions who cannot adequately be treated with other locally approved iron chelators.
05/12/2005	New Investigator to Study No. 0109E1: Drs. K.L. Hassell, R. Nuss.
05/12/2005	Teleconference with FDA to discuss treatment protocol.
05/18/2005	Amendment No. 5 to Study No. 0109: Amendment No. 1 to Study No. 2201: Amendment No. 2 to Study No. US02.
05/18/2005	This submission responds to a request to submit a copy of the informed consent and the Investigator's Brochure in support of the protocol submitted May 12, 2005, Serial No. 226.

05/23/2005	New Investigator to Study No. 0109E1: Dr. Andrew S. Freiberg. Study No. 0117: Drs. Vichinsky, L. Rice. Study No. 2201: Drs. L. Krishnamurti, C. Tebbi, A.A. Thompson, M.J. Haut. Study No. US03: Dr. J.M. Feigert.
05/31/2005	FDA letter regarding treatment use under the treatment protocol received May 13, 2005.
06/06/2005	Facsimile from FDA containing comments from the review of the informed consent document for a treatment protocol.
06/06/2005	Teleconference with FDA to discuss the Division's comments on protocol 2203 and the informed consent.
06/07/2005	Clinical information submission containing final reports for studies: 0105, 0106, 0107, 2121, 2122, 0107 and 0108.
06/07/2005	Revised treatment protocol 2203 and informed consent in 232 response to comments made at the June 6, 2005 teleconference.
06/07/2005	Teleconference with FDA regarding revised treatment protocol 2203 and Informed Consent.
06/08/2005	New Investigator to Study No. 109E1: Dr. L. Krishnamurti. Study No. 0117: Drs. P. Kelly, G. Puthenveetil. Study No. 2201: Drs. M.F. Gonzales, M. Blinder, M.T. Lee.
06/09/2005	FDA letter stating that there is no objection to the May 12, 2005 proposed treatment use of this drug.
06/09/2005	Facsimile from FDA containing a safe to proceed letter for Serial No. 226.
06/13/2005	Amendment No. 2 to Study No. 0109E1.

07/07/2005	New Investigator to Study No. US02: Dr. Charles Schiffer. Study No. US03: Dr. Pradyumna Phatak. Study No. 109E1: Drs. C. Roberts, M. Heeney, A.A. Thompson. Study No. 117: Dr. Rita Bellevue. Study No. 2201: Drs. O. C. Onyekwere, R.L. Wise, W.C. Owen, M. Heeney, M. Torres.
07/15/2005	New Investigator to Study No. 0109: Drs. R. Wise, V. Deas; Study No. 0109E1: Drs. O.C. Onyekwere, V. Deas, T. Coates, P. Pederzoli, T. Tran.
07/21/2005	Dr. Zahida Yasin: Pulmonary embolism, lobar pneumonia, night sweats, feeling hot, thrombosis, concomitant disease progression, chest pain, dyspnoea; Follow-up #2.
07/26/2005	New Investigator to Study No. US03: Drs. S. Goldberg, E. Rich; Study No. 109E1: Drs. P.S. Swedlow, R. Gardner, Latha Prasannan; Study No. 2201: Drs. A. Kutlar, C.D. Scher, C. Minniti, W. Smith
08/12/2005	New Investigator to Study No. US03: Dr. S. Ganguly. Study No. 109E1: Drs. F.L. Wilson, P. Lane, L.J. Benjamin, T. Coates, P.J. Giardina, L. Mathias, J. Kwiatkowski, B.U. Mueller. Study No. 2201: Drs. R.J. Labotka, L. Mathias, A. Christodoulou-Pefkarou, S. Rao, Z. Yasin, J. Glass.
08/18/2005	Amendment No. 4 to Study No. 0108E1.
08/25/2005	Amendment No. 4 to Study No. 0107E1.
08/30/2005	Annual Report covering the period July 1, 2004 through June 30, 2005. Includes clinical study information, preclinical information and CMC changes.
08/31/2005	Amendment No. 1 to Study No. US03.
09/14/2005	New Protocol to Study No. US04 entitled "An open label trial evaluating cardiac T2 in B-thalassemia patients on deferasirox (ICL670) treatment for 18 months.

09/14/2005	New Investigator to Study No. US03: Drs. E. C. Besa, B. Powell, A. Raza, L. Rice, W.G. Harker; Study No. 2201: Drs. R. Gardner, A.D. Campbell.
09/21/2005	New Investigator to Study No. US02: Dr. C.A. Koller. Study No. US03: Drs. K. McDonagh, S. Cataland, N.J. DiBell, D.P. Steensma, K.R. Meehan. Study No. 0107E1: Dr. M.R. Jeng. Study No. 2201: Drs. E. Vichinsky, M. Heiny, B. Files, R.P. McCaffrey, L.S. Frankel, J.P. Cain, L. Hillard.
10/10/2005	New Investigator to Study No. US02: Dr. P. Greenberg. Study No. US03: Drs. C. Chay, J.R. Eckardt, B. Kaplan, A. Moreno-Aspitia. Study No. 109E1: Drs. M. Jeroudi, R. E. Ware. Study No. 2201: H.I. Saba. Study No. 2203: Dr. B. Lewis.
10/10/2005	Amendment No. 1 to Study No. 2203.
10/10/2005	New Investigator to Study No. US02: Dr. P. Greenberg. Study No. US03: Drs. C. Chay, J.R. Eckardt, B. Kaplan, A. Moreno-Aspitia. Study No. 109E1: Drs. M. Jeroudi, R. E. Ware. Study No. 2201: H.I. Saba. Study No. 3303: Dr. B. Lewis.

NDA PERIOD

12/15/2004	Teleconference with the FDA for a preassigned NDA number (NDA 21-882).
01/04/2005	Teleconference with FDA regarding filling out the user fee sheet and 356H form since the application is a rolling submission.
01/10/2005	This submission contains a Reviewable Unit (RU) for the CMC section of the original application. The remaining sections will be submitted in April 2005. ICL670 is indicated for the treatment of chronic iron overloaded due to blood transfusions [1CD; electronic submission in REDI].
01/12/2005	Emails to/from FDA regarding an Advisory Committee Meeting.
01/26/2005	FDA letter acknowledging receipt of the reviewable unit of the CMC section of the original NDA for ICL670A (deferasirox) tablets, dated January 10, 2005.
04/29/2005	In reference to the January 10, 2005 submission of the CMC Reviewable Unit, this submission completed the original NDA application.
05/10/2005	CMC Amendment provides for updated product stability data.
05/16/2005	Teleconference with FDA regarding applicant orientation meeting scheduled for June 29, 2005.
05/20/2005	Response to request for information regarding patient enrolment by study center for studies 0107, 0108, and 0109 (paper submission).
05/27/2005	In reference to the reviewable unit (CMC) submitted January 10, 2005 this submission contains Quality Overall Summary documents that were missing from that application.

06/03/2005	E-Mail to FDA regarding the agenda for the June 29, 2005 NDA orientation meeting, specifically the outline of clinical data presentation.
06/07/2005	Teleconference with FDA regarding revised treatment protocol 2203 and Informed Consent.
06/13/2005	Teleconference with FDA to discuss that ICL670 would be brought to the Blood Products Advisory Committee because it was a New Molecular Entity. FDA also reinforced that the Division would meet with NVS prior to the Advisory Committee meeting to discuss contents and issues that will be discussed at the meeting. FDA confirmed that the Priority Review Letter will be sent out within a week of this conversation.
06/17/2005	FDA letter acknowledging receipt of original NDA.
06/21/2005	Facsimile from the FDA requesting preclinical information, specifically datasets for the 2-year rat carcinogenicity study #17022 and the 26-week oral gavage carcinogenicity study in p53 hetergygous.
06/21/2005	Teleconference with FDA to discuss the applicant orientation meeting scheduled for June 29, 2005.
06/24/2005	E-mail to FDA listing the NVS attendees for the June 29, 2005 Advisory Committee Meeting. Additionally, NVS confirmed that the preclinical datasets, requested by FDA on June 21, 2005, will be FedExed by July 1, 2005 in electronic format.
06/29/2005	Minutes of the June 29, 2005 Applicant orientation review meeting (NDA review) with the Division of GI/Coagulation drug products.
06/29/2005	Response to FDA request for datasets for the 2-year rat carcinogenicity study #17022 and the 26-week oral gavage carcinogenicity study in p53 hetergygous mice.

07/07/2005	FDA Discipline Review Letter identifying deficiencies in the Drug Substance, Drug Product and Labeling sections of the Exjade NDA submitted under the Continuous Marketing Application (CMA)-Pilot-1 program.
07/08/2005	Amendment to a pending application providing the final juvenile mouse toxicology report 0480148. The version submitted in the original NDA has undergone QA by NVS and no changes to the results or conclusions have resulted by this QA. The only changes were editorial in nature.
07/11/2005	Facsimile from the FDA requesting the historical control data for the carginogenicity rat study 017022 and mouse study 0270117 covering 3-5 years prior to the end of the in-life phase.
07/11/2005	Response to FDA request for information confirming that Exjade is not marketed in any country at this time.
07/12/2005	Emails to/from FDA for the period covering June 24 through July 12, 2005 regarding the list of NVS attendees for the June 29, 2005 review meeting. It further discusses NVS June 29, 2005 response to FDA's request for historical control data for the carcinogenicity rat study 017022 and the study in p52 mice.
07/14/2005	FDA Filing Communication Letter advising that FDA has completed the filing review of the new drug application and that it is sufficiently complete to permit a substantial review. FDA also identified potential review issues pertaining to the clinical information.
07/18/2005	Teleconference with FDA, Blood Products Advisory Committee, regarding the September 29, 2005 advisory committee meeting.
07/28/2005	Amendment to a Pending NDA (CMC) is in response to FDA e-mail, dated 21-Jul-2005, requesting submission of the categorical exclusion document of the environmental assessment.

08/03/2005	Teleconference with FDA during which was discussed the tentative agenda and logistics for the September 29, 2005 advisory committee meeting.
08/11/2005	Teleconference with FDA advising that they could not locate the SAS data sets for the rat carcinogenicity data. As per the FDA reviewer, it appeared that only the mouse data was included in the June 29, 2005 reply to a request for information. The rat carcinogenicity SAS data sets were submitted on CD-ROM to FDA via FedEx on August 15, 2005.
08/15/2005	This correspondence includes the SAS data sets for the rat carcinogenicity data requested by FDA and is a follow-up to the June 29, 2005 FDA request for information.
08/26/2005	Briefing Book submitted to FDA/CDER/SACS in paper and electronically for the blood products advisory committee meeting scheduled for September 29, 2005 for the proposed indication of the treatment of chronic iron overload due to blood transfusions in adults and pediatric patients.
08/29/2005	E-submission of the 120-day safety update.
09/08/2005	E-Mails to/from FDA containing the redacted FDA background package for the September 29, 2005 Blood Products Advisory Committee meeting.
09/09/2005	Facsimile from the FDA regarding CDRH reviewer's request for clarifications concerning BLS measurements using the SQUID magnetometer.

09/12/2005	Teleconference Pre-AC meeting to discuss presentations for the September 29, 2005 Blood Products Advisory Committee meeting. The focus was mainly on the pivotal study 0107, but commented that similar slides would be shown for studies 0108 and 0109. In response to FDA's inquiry regarding the efficacy data for study 0109, which was not presented in the NDA, NVS stated that it was submitted in the 120-day safety update. FDA stated that these data could only be brought in if there were a second review cycle or later as a supplement.
09/12/2005	FAX from FDA transmitting the meeting roster for the Pre-AC meeting scheduled for September 12, 2005.
09/16/2005	General Correspondence: Response to Information Request addresses the CDRH reviewer's request for clarifications concerning BLS measurements using the SQUID magnetometer.
09/19/2005	Email to FDA responding to request for a table, which provides an accounting of patients treated with ICL670 that was included in the NDA.
09/19/2005	PAD, C-ICL-1001 Coming Soon Ad, PLT, ICL-1004 Coming Soon teaser.
09/20/2005	General Correspondence: Response to Information Request addresses the CDRH reviewer's request for clarifications concerning BLS measurements using the SQUID magnetometer.
10/03/2005	TELECON with FDA regarding post-approval commitments. FDA outlined several criteria that the sponsor must meet with accelerated approval process. NVS confirmed the October 18 telecon with FDA to discuss commitments, at which time, NVS also confirmed that the PI submitted with the 120-day safety update, should be used for FDA review.

10/05/2005	E-MAIL to FDA as a follow-up to October 3, 2005 teleconference regarding clarification of post-approval commitments, namely, biopsy issue, the issue of safety in children 2-6 years, and accelerated approval impact on promotional materials, due to the lack of the final labeling.
10/06/2005	TELECON with DDMAC regarding pre-clearance of all promotional pieces as a commitment of the accelerated approval process. NVS informed DDMAC that we were not aware that Exjade would be undergoing accelerated approval and that on September 19, 2005, NVS submitted a Coming Soon AD and a Coming Soon Teaser upon first use.
10/12/2005	E-MAILS to/from FDA regarding proposed labeling, specifically dosage and administration section.
10/14/2005	This submission contains draft professional promotionai material Expanded PI (ICL-OT-0031-A); Coming Soon Panel (ICL-EX-0058-A); Now Available Panel (ICL-EX-0030-A); Promotional Giveaways (ICL-PM-0065-A, ICL-PM-0065-B, ICL-PM-0065-C, ICL-PM-0065-D, ICL-PM-0065-E); Exjade Website Homepage - Version 1 (ICL-WS-0067-A).
10/18/2005	TELECON and meeting minutes from teleconference of October 18, 2005 with FDA regarding the Post-Approval Commitments.
10/19/2005	This submission is in response to FDA's post-approval commitment request for analyses of biopsy data on size and correlation with success rates, serum ferritin, and LIC. In addition, this submission constitutes the official copy of documentation sent to FDA via secure e-mail on October 17, 2005.
10/20/2005	TELECON with DDMAC requesting the review status of draft promotional material submitted October 14, 2005.
10/21/2005	E-MAIL from FDA regarding post-approval comments and instructions to disregard two comments, which have been addressed.

10/21/2005	TELECON with DDMAC regarding DTC promotional material. NVS plans to submit DTC pieces by the end of October or early November.
10/21/2005	This submission contains post-approval commitments based on comments received during the October 18, 2005 teleconference. In addition, this documentation constitutes the official copy of information sent to FDA via secure e-mail on October 21, 2005.
10/24/2005	TELECON w/DDMAC regarding professional promotion materials. DDMAC encouraged NVS to submit all our materials before the approval date, even though the label is not finalized, in order to avoid being locked out of using promotional materials during the 120 day post-approval.
10/25/2005	E-MAILS to/from FDA regarding the revised version of the post-approval commitments, as well as the dosage and Administration sections of the PI. FDA requested information on what is the mg/mL concentration after reconstitution for each vial size for each diluent amount to be added and what is the amount of total drug content after reconstitution.
10/25/2005	E-MAILS to/from FDA regarding comments received on the labeling received October 21, 2005, specifically the information contained within the parentheses, as well as the additional language added (do not chew or swallow whole). FDA confirmed that the language should be included and that the established name should appear in the parentheses.
10/27/2005	This submission contains revised draft labeling, as per FDA comments of October 21, 2005. The PI was sent to FDA via secure e-mail on October 26, 2005 and this submission constitutes the official copy.

10/27/2005	E-MAILS to/from FDA responding to FDA's request for information on what is the mg/mL concentration after reconstitution for each vial size for each diluent amount to be added and what is the amount of total drug content after reconstitution.
10/31/2005	This submission contains draft professional promotional materials for informational use only.
10/31/2005	This submission contains draft Direct-to-Consumer (DTC) promotional material.
10/31/2005	This submission contains Direct-to-Consumer (DTC) promotional material for informational use only.
10/31/2005	This submission contains draft professional promotional material.
11/01/2005	E-MAILS from FDA regarding post-approval commitments and language included in the PI.
11/01/2005	E-MAILS from FDA confirming that comment #5 does need study start and final report submission, as well as rewording.
11/01/2005	This correspondence contains revised draft labeling and post-approval commitments, which were received from FDA on October 28, 2005. This submission constitutes the official copy of these documents, which were sent to FDA via secure e-mail on October 31, 2005.
11/01/2005	This letter is to clarify that the EXJADE professional promotional materials submitted on October 14, 2005 were mistakenly submitted with FDA form 2253, when the intent of the submission is for Advisory Comments per sub-part H.
11/02/2005	E-MAIL from FDA containing the approval letter and approved PI.
11/02/2005	E-MAILS to/from FDA regarding PMC PIT and revisions to the PI.

11/02/2005	E-MAIL responding to FDA request for information on the NOEL study number 971974 for the PAC-PI commitment.
11/03/2005	FDA LETTER responding to NVS request for comments for proposed launch advisory submitted on October 14, 2005. These comments are provided using a draft version of the labeling and DDMAC advises NVS to update promotional materials to reflect the information available in the final approved PI. MACMIS ID # 13812
11/04/2005	TELECON from DDMAC confirming receipt of the Exjade launch DTC materials. However, FDA comments would not be received within 30 days.
11/04/2005	This correspondence contains a waiver request under CFR 314.90(a) to submit Form 3500A for adverse experiences determine to be both non-serious and labeled in the periodic safety report.
11/04/2005	TELECON with DDMAC to confirm receipt of the launch DTC materials. DDMAC stated that there is a backlog at DTC and would not be able to furnish comments within 30 days.
11/07/2005	TELECON w/DDMAC regarding advisory comments on the promotional pieces submitted on October 14, 2005.
11/08/2005	E-MAIL to FDA requesting information from the Agency regarding updated information for the PI and the correct method to report the changes.
11/08/2005	TELECON with DDMAC DTC group regarding the launch of the DTC materials. DDMAC requested that NVS identify which pieces were highest priority. NVS will identify the 5-6 priority items for DDMAC review and comment.
11/10/2005	PAD, ICL-AD-0018A Journal Ad. PEP, ICL-EX-0030A Convention panel.

11/15/2005	Final printed labeling for approved NDA 21-882. There was a minor editorial change made to the package insert included in the approval letter of November 2, 2005, regarding the tablet imprint. This minor change will be described in the annual report.
11/16/2005	E-MAIL to DDMAC-DTC group identifying the priority items for advisory comments.